Suicidal Behaviour in Early Psychosis
The Role of Insight

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Suicidal Behaviour in Early Psychosis.

The Role of Insight

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Dedication

En agradecimiento y con mucho cariño a mis padres, Miguel Ángel y María Esperanza, cuyo recuerdo pervivirá para siempre en estas páginas.

Y a Encarna, por un presente y futuro juntos.

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My main thanks go to the studies participants. They have made this research possible and they should be the main recipients of its potential implications. Also, my thoughts are with those who took their lives. If the effort behind this thesis could contribute to preventing one such death in the future, it will have been worth making.

My supervisors, Professor Anthony David and Dr Rina Dutta, have provided not only the academic assistance necessary throughout my PhD, but also their personal kindness and support as required. In addition, Professor Sir Robin M. Murray and Dr Marta Di Forti (GAP main investigators), Professor Craig Morgan (AESOP principal investigator), Professor Rob Stewart (CRIS project co-founder), Professor Benedicto Crespo-Facorro and Dr Rosa Ayesa-Arriola (Santander lead researchers) deserve my recognition for kindly sharing data from their research projects with me, which was fruitfully incorporated in this thesis.

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From a more personal perspective, this work is dedicated to my family, particularly my parents, Miguel Ángel and María Esperanza, and my uncle, Dr Ángel Moríñigo Domínguez, who rightly encouraged me to move to London and embark on an academic career. Sadly, my mother, Esperanza, which means hope in Spanish, deceased in the middle of this PhD. She will not be able to read her son's thesis, but her loving memory will lie forever on these pages. In addition, other loves (Irene, Claire and David) have passed away over these six years. This work pays tribute to them as well.

My friends, thankfully too numerous to mention by name, should take some credit for this PhD. They were a great blessing to me during the above difficult times, thus contributing to this success.

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Abstract

Early psychosis is a high-risk period for suicide. Of concern, suicide rates in psychosis have increased over recent years. Several risk factors have been established, including being male, white, recent loss, previous suicide attempts, depression, illegal drug use and agitation/restlessness.

Although insight has been consistently associated with positive outcomes in psychosis, concerns have been voiced regarding the potential link between insight and increased suicidality. Thus, this thesis commences with a literature review on this topic, which reported mixed results and methodological limitations in previous studies, which were addressed in this investigation.

Real-world data on suicides by patients with schizophrenia from the South London and Maudsley NHS Foundation Trust are also presented, which supports further the necessity for this work.

Data from three large cohorts of first-episode psychosis (FEP) patients from the UK (n=112-181) and Spain (n=397) were analysed to ascertain the role of multiple insight dimensions (illness recognition, symptoms relabelling, awareness of the social consequences and awareness of the need for treatment) in risk for suicidal behaviour. Although bivariate analyses showed significant relationships between insight levels and risk of suicidal behaviour, only previous suicide attempts and depression, both of which were linked with insight, survived the multivariate analyses, hence emerging as the main predictors of suicidal behaviour. In other words, suicidal history and depression appear to explain the apparent association of insight with suicide risk in psychosis.

Hence, no evidence was found supporting a *direct* relationship between insight and suicidal behaviour in early psychosis despite common assertions to the contrary, which has implications on clinical practice and future research. Insight, which is linked with better outcomes, does not increase suicidality. Guidelines should therefore prioritise improving insight interventions (e.g. talking therapies or antipsychotics) from first presentation with psychosis and future studies may examine whether this reduces suicide rates.

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List of abbreviations and definitions

A&E	Accident and Emergency Department
AESOP	Aetiology and Ethnicity of Schizophrenia and Other Psychoses study
BRC	Biomedical Research Centre
CDSS	Calgary Depression Scale for Schizophrenia (Addington et al., 1992)
CI	Confidence Interval
CRIS	Clinical Record Interactive Search (Stewart et al., 2009)
CTO	Community Treatment Order
DSM	The Diagnostic and Statistical manual of Mental disorders
DUP	Duration of Untreated Psychosis
FEP	First-episode psychosis
GAP	Genetics and Psychosis study
HoNOS	Health of the Nation Outcome Scale (Wing et al., 1994)
ICD	International Classification of Mental and Behavioural Disorders
IMI	Insight into mental illness
INT	Insight into the need for treatment
ISC	Insight into the social consequences of the illness
MHA	Mental Health Act
ONS	Office for National Statistics
OR	Odds Ratio
PANSS	Positive and Negative Symptoms Scale (Kay et al., 1987)

RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SA	Suicide attempt. A potentially self-injurious behaviour with a nonfatal outcome, for which there is evidence (either explicit or implicit) that the person intended to kill him/herself' (O'Carroll et al., 1996)
SAI-E	Schedule for Assessment of Insight (Kemp & David, 1997)
SAPS	Scale for the Assessment of Positive Symptoms (Andreasen, 1983)
SANS	Scale for the Assessment of Negative Symptoms (Andreasen, 1983)
SC	Suicide completion. Death from injury, poisoning, or suffocation where there is evidence (either explicit or implicit) that the injury was self-inflicted and that the decedent intended to kill him/herself' (O'Carroll et al., 1996)
SCAN	Schedule for Clinical Assessment in Neuropsychiatry (WHO, 1992)
SLaM	South London and Maudsley NHS Foundation Trust
SPSS	Statistical Package for the Social Sciences
SSD	Schizophrenia Spectrum Disorder
SUMD	Scale to assess Unawareness of Mental Disorder (Amador, 1993)
TMT	Trail Making Test (Reitan, 1958)
WAIS	Wechsler Adult Intelligence Scale (Wechsler, 1981)
WHO	World Health Organization

Personal Contribution

Data for this PhD were taken from the Genetics and Psychosis (GAP) Study and the Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study at the Institute of Psychiatry, Psychology and Neuroscience (King's College London). In particular, I was involved in recruitment and general baseline assessment (which included clinical and insight assessments) of GAP patients in the early stages of my PhD. In addition, I contributed to collecting follow-up data, including suicidal behaviour variables. With regard to the AESOP study, I cleaned up previously created datasets to select those patients with the relevant information available for this PhD, namely insight and suicidal behaviour variables.

In addition, I was involved in the large Clinical Records Interactive Search (CRIS) project, particularly in the ongoing large suicide project.

Finally, I participated in the Santander (Spain)-based FEP program called PAFIP. In particular, I contributed to cleaning the database and conducting the statistical analyses.

I carried out all of the data analyses presented in this thesis and I drafted all the chapters.

Chapter 1 - General introduction

*'There is but one truly serious philosophical problem and that is **suicide**'.*

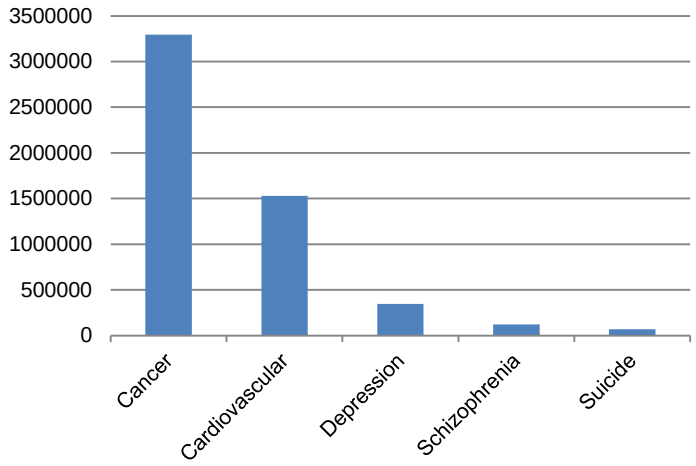
The Myth of Sisyphus, Camus A. (1942)

(trans. from French: Le Mythe de Sisyphe by O'Brien, J. (1955)

In 'The Myth of Sisyphus', Camus suggests that *suicide* amounts to a confession that life is not worth living (the basis of a common question asked to patients in routine clinical practice). In other words, Camus linked suicide with what he called the 'absurd', i.e. the meaninglessness of life. Can peoples' lives change to become more meaningful? Is suicide preventable? In short, the answer has to be 'yes' (WHO, 2016), otherwise, why would anyone bother investigating the topic further?

Although every year almost one million people end their lives across the world - it has become one of the three leading causes of death in the most economically productive age group (15-44 years) (WHO, 2016) - suicide has received relatively little attention in medical research. For example, a simple search on Medline accessed on 15 May 2016 by using five 'Medical Subject Headings', including suicide, yielded the following results, graphically shown in figure 1.1. below:

Figure 1.1. Medline search for the following Medical Subject Headings: 'cancer', 'cardiovascular', 'depression', 'schizophrenia', 'suicide' (accessed on 15 May 2016)



One potential reason for this disparity is that from a historical perspective, suicide was still a criminal offence in many countries until relatively recent times; for instance, suicide was only decriminalised in the UK in 1961 (UK Government, 1961). Indeed, in contemporary society suicide is still prosecuted (at least in theory) in up to 23 countries (WHO, 2016). Also, the public used to consider suicide a sin, although no religion, including Islam and Christianity, specifically condemns suicide (Berrios, 1996). On the other hand, suicide is still accepted as a normal behaviour by some minorities such as the Jaina Sect in India and The Yurubas in Nigeria (Berrios, 1996). Moreover, ethnic differences in risk of self-harm and suicide have been consistently found both in the UK (see Al-Sharifi et al., 2015) and in other countries (e.g. McKenzie et al., 2012), which in psychosis appear to be mediated by factors such as religion, cultural appraisals of illness and social aspects (Upthegrove et al., 2013). Thus, suicide research in psychosis should consider the influence of cultural-related variables by cross-comparing findings from samples from different countries and backgrounds, which is the approach taken by this investigation, which includes psychosis patients from the UK (diverse ethnicities, including ethnic minorities, with different religions) and Spain (Caucasian white people, mainly Christian). See chapters 4-8 for further details.

Figure 1.2. Suicide Act 1961 (Taken from UK Government, 1961)

Hence, in my opinion the limited research on suicide to date seems to be related to issues around stigma (not only stigma towards mental health in general, but particularly towards suicide), including stigma from colleagues within the medical field. In addition, the funding support for research in mental health is scant when compared with other disciplines, such as cardiology or oncology, which may explain, to some extent, the data shown in figure 1.1. above.

What is the role of psychiatry in suicide prevention?

Psychological autopsy studies have revealed that about 90% of people who killed themselves had a mental disorder (Arsenault-Lapierre et al., 2004), which accounts for up to 47-74% of the population attributable fraction (Cavanagh et al., 2003), with depression and psychotic disorders the most common diagnoses found in suicide completers (Arsenault-Lapierre et al., 2004). With regard to psychosis, the early stages of the illness have been consistently found to be the highest risk period (e.g. Palmer et al., 2005), and I will discuss this in more detail throughout this thesis. However, others argue that suicide in schizophrenia might be a rational act in some individuals (Hewitt et al., 2010), which was also Bleuler's view quoted below (Bleuler, 1911).

Thus, this chapter begins with some information on the concept of psychosis, with a focus on early psychosis. Then, the next section reviews the definition of suicidal behaviour, including suicide attempts and suicide completion, and summarises the epidemiology of suicide both in the general population and in psychosis. In keeping with this, chapter 3 provides new clinical data on suicide in patients with schizophrenia spectrum disorders who received secondary mental healthcare in the South London and Maudsley NHS Foundation Trust. The third section of this chapter deals with insight from a historical/conceptual perspective and also, it presents some of the measures which will be used in this thesis. Then, in chapter 2 I formulate the specific research question of this thesis and I explain its clinical relevance, including an updated systematic literature review on this topic. In addition, I postulate my *a priori* responses to this question, i.e. the hypotheses which will be tested with data from two first-episode psychosis (FEP) samples (presented in chapters 4-7), before drawing a reasoned conclusion as discussed in chapter 8.

1.1. – Psychosis

1.1.a. – History

Clinicians, including those who work in areas other than mental health, often receive referrals or reports in which a patient is described as '*psychotic*' or suffering from *'psychosis'*. From this, the clinician immediately becomes aware that the patient suffers from a *severe mental disorder* with a range of symptoms which can be *explained*, but *never understood*, as Jaspers stated in 1913 (Jaspers, 1913).

Psychosis (from the Greek, '*any illness of the mind*') was first coined by the Austrian poet and physician Ernst von Feuchterlesben in his 1845 publication 'The Principles of Medical Psychology' to describe a wide range of mental disturbances characterized by '*a confusion between the self and the world*', i.e. '*a confusion between the body and the mind*'.

Over the second half of the 19th century, several contributions from French and German schools to better understanding psychosis resulted in the categorical classification of psychotic disorders developed by Emil Kraepelin (1856-1925) in 1896. Thus, Kraepelin clinically observed that his patients could be classified into what he determined were two different, mutually exclusive, categories. Thus, those who suffered from three previously described nosological entities, namely Démence précoce (Morel, 1809-1873), catatonia (Kahlbaum, 1828-1899) and hebephrenia (Hecker, 1843-1909), were reported to have a similar deteriorating course of the illness with poor early outcomes. Subsequently, Kraepelin combined these three syndromes into a single disease entity which he coined *dementia praecox*, meaning 'senility of the young'. On the other hand, those patients with the so-called *manic-depressive illness* presented with a remitting-relapsing condition which included periods of full recovery and a favourable long-term prognosis (Kraepelin, 1896).

In the first decades of the 20th century, when no effective psychiatric medication was available, most therapies for mental disorders were based on emerging ideas from Freud's psychoanalysis. Thus, another German-speaking Swiss psychiatrist, Eugen Bleuler (1857-1939), who was highly influenced by psychoanalysis via two of his trainees, Adolf Meyer and Carl Gustav Jung, attempted to explain the psychotic phenomenology observed on his institutionalised patients through the interpretation of their experiences of the self, thus coining the term *schizophrenia* (from Greek, 'split mind'). Given the severity of their symptoms and the lack of effective treatments at that point, Bleuler took a more psychodynamic approach in order to alleviate their suffering. Like Kraepelin, Bleuler argued that dementia

praecox, or "group of the schizophrenias", was fundamentally a physical disease process characterized by exacerbations and remissions. Although Bleuler agreed that no one was ever completely "cured" of schizophrenia, he believed that the overall prognosis was not uniformly grim. Bleuler listed four primary symptoms of schizophrenia, which were traditionally taught to medical students as the four "As", namely Autism, Ambivalence, loosening of Associations and inappropriate Affect. Bleuler's son, Manfred Bleuler, considered that the main contribution made by his father to the problem of schizophrenia(s) was "*to favour the study of what was going on 'psychodynamically' in a schizophrenic patient.*'' (Bleuler, 1983).

Later in life, Kraepelin himself raised concerns about the limitations of his dichotomous classification (Kraepelin, 1920):

"*No experienced psychiatrist will deny that there are an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis… Nevertheless it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect*."

However, Kraepelin's chief pupil, Carl Wernicke (1848-1905), mainly focused on neurology, particularly on aphasia. Wernicke postulated a 'theory of disjunction', that is, an interruption of the connections between neural systems to explain psychopathology. This led to him receiving criticism from Karl Jaspers (1883-1969) who labelled Wernicke a 'brain mythologist'. At age 28 Jaspers wrote his seminal contribution to psychiatry, General Psychopathology (Jaspers, 1913), a comprehensive description of mental symptoms from a phenomenological perspective. Unfortunately, Wernicke died prematurely and he did not have many students of psychiatry. Only Kleist took up his ideas, which were widened further by Karl Leonhard (1904-1988), a pupil of Kleist. Thus, the so-called 'Wernicke- Kleist Leonhard' School developed a classification of endogenous psychoses originally published in 1957 (Leonhard, 1979), which included up to five categories (phasic psychoses, cycloid psychoses, unsystematic schizophrenias, systematic schizophrenias and childhood onset schizophrenias), each of which had a number of different subtypes. Interestingly, findings from genetics based on twin studies (Franzek & Beckmann, 1998) appear to provide further support for this first classification of psychoses from a dimensional approach. Also, a recent study demonstrated the Leonhard's Classification to have a higher degree of familial aggregation than the DSM-IV-TR (APA, 2000) or ICD-10 (WHO, 1993), which may be therefore better suited for molecular genetic studies than the official diagnostic systems (Peralta et al., 2016).

After the Second World Ward and the "euthanasia" era in Germany, from which Leonhard himself saved many patients, German psychiatry became discredited and turned towards more psychodynamic approaches such as psychoanalysis. In addition, the relative isolation of Leonhard during the latter part of his life in East Germany, after the partition of Germany in 1961, prevented the Wernicke-Kleist-Leonhard School's contributions from receiving much attention in Western countries. However, the first lines written by Leonhard in the seventh edition of his 'classification of endogenous psychoses' may still explain the relatively low success from decades of neurobiological research on psychoses (Leonhard, 1979):

"…Lack of success in clinical etiological research in my opinion is the result of the fact that endogenous psychoses have been roughly divided into only two forms. In this way a majority or even a multitude of disorders have been lumped together and therefore no uniform aetiology could of course be found…."

Another German psychiatrist, Kurt Schneider (1887-1967), who had been Jaspers' pupil, highlighted the organic origin of all types of psychoses in his 1946 Clinical Psychopathology (see Schneider, 1959). In addition, Schneider listed a group of symptoms, which were found to be highly specific, but not pathognomonic, of schizophrenia as opposed to other psychoses (Peralta & Cuesta, 1999). These were called 'first-rank' symptoms (see table 1.1. below) and as a whole, they concern the inability to identify the boundaries between the self and the non-self. The first-rank symptoms have been highly influential on the current classifications of mental disorders, such as the International Classification of Diseases (10th edition) (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition, (DSM-5) (APA, 2013).

Table 1.1. Schneider's first-rank symptoms

Hearing thoughts spoken aloud
Hallucinations: third-person, somatic or in the form of a commentary
Thought withdrawal, thought insertion or thought broadcasting
Delusional perception
Feelings or actions experienced as made or influenced by external agents

The value of the term 'psychosis' is that it is a more inclusive category than 'schizophrenia', yet it implies serious impairment. More recently, the term 'schizophrenia spectrum disorders' has been widely accepted due to its broader meaning and less stigmatising connotations, which also tends to include those patients with schizoaffective disorder.

1.1.b. – Current classification of psychotic disorders

As detailed above, Kraepelin and Schneider have significantly influenced the current international classifications of psychotic disorders in ICD-10 and DSM-5. However, there are some minor differences between these two approaches, which are typically used in Europe and America, respectively. Thus, while the ICD-10 criteria put more emphasis on the Schneiderian first-rank symptoms, the DSM-5 approach is more focused on the duration of symptoms and their impact on psychosocial functioning. Main diagnostic categories of DSM-5 psychotic disorders are listed in table 1.2. below and the specific diagnostic criteria for schizophrenia are shown in box 1.1.

Table 1.2. Main diagnostic categories of DSM-5 psychoses (APA, 2013)

- Schizophrenia
- Schizoaffective disorder
- Schizophreniform disorder
- Delusional disorder
- Brief psychotic disorder
- Catatonia
- Attenuated Psychosis Syndrome and Shared Psychotic Disorder
- Bipolar I Disorder (with psychotic features)
- Bipolar II Disorder (with psychotic features)
- Cyclothymic Disorder (with psychotic features)
- Major depressive disorder (with psychotic features)
- Psychotic disorder due to a general medical condition
- Alcohol-induced psychosis
- Other substance-induced psychosis

Box 1.1 – DSM-5 diagnosis of schizophrenia

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

--delusions

--hallucinations

--disorganized speech (e.g. frequent derailment or incoherence)

--grossly disorganized or catatonic behaviour

--negative symptoms, i.e., affective flattening, alogia, or avolition

Note: At least two of the five symptoms must be present for at least one month. One of the two symptoms *must* be delusions, hallucinations, or disorganized speech.

B. Social/occupational dysfunction: The level of functioning, including areas such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive Episode, Manic Episode, or Mixed Episode have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

F. Relationship to an Autism Spectrum Disorder or Communication Disorder: If there is a history of Autistic Disorder or another Communication Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

1.1.c. – Dimensions vs. Categories. What are the symptoms of psychosis?

In keeping with the Leonhard's model of psychoses proposed in 1957 (see Leonhard, 1979), recent research has suggested that the phenomenology of psychotic disorders, including first presentation with psychosis (Peralta et al., 2013), may be better conceptualized by several symptom dimensions (van Os, 1997; Peralta & Cuesta, 2001; Demjaha et al., 2009), namely positive (e.g. delusions and hallucinations), negative (e.g. apathy, blunted affect, social isolation), disorganization (e.g. loosening of association, derailment, flight of ideas), mania (e.g. elation, euphoria, overfamiliarity, disinhibition) and depression (e.g. low mood, anhedonia) (Peralta & Cuesta, 2001; Demjaha et al., 2009), and catatonia, agitation and lack of insight (Peralta & Cuesta, 2001).

Of particular interest to this investigation is the concept of depression in psychosis. Although Kraepelin (1896) had considered schizophrenia to be a 'non-affective' psychosis, recent research suggests otherwise (e.g. Peralta et al., 2013). Thus, up to three pathways have been proposed to link depression with schizophrenia: i) depression as intrinsic to psychosis; ii) depression as a psychological reaction to the diagnosis (which links with my main research question, as explained below); and iii) depression in psychosis in relation to childhood trauma, i.e. as confounder since childhood trauma is associated with psychosis (Trotta et al., 2015) and depression (for a review, see Bebbington et al., 2005; Upthegrove et al., 2016).

Also, despite findings from neurobiological research supporting a dimensional model of psychoses (Craddock & Owen, 2010), the official international classifications ICD-10 and DMS-5 are still based on the 'first' Kraepelinian dichotomy. Thus, schizophrenia and affective psychoses are still mutually exclusive diagnoses (see box 1.1. above).

1.1.d. – Psychosis and schizophrenia

Although from a historical point of view, schizophrenia represents the paradigm of psychotic disorders, caution should be taken when using these two terms interchangeably. Thus, it should be noted that schizophrenia does not necessarily equate to psychosis and vice versa. However, research and treatment focused on a broader concept of psychosis has several advantages. Specifically, recent research findings from genetics suggest that psychotic disorders are overlapping, rather than separate entities (Owen et al., 2011). Also, diagnosis can

change within the psychosis spectrum over time, although schizophrenia is usually found to have the highest stability (e.g. Bromet et al., 2005).

In order to briefly discuss the aetiology of psychotic disorders as part of this chapter, most of the research findings presented below come from studies on schizophrenia. Indeed, research on psychosis and schizophrenia is often treated as interchangeable despite being based on different concepts. Moreover, this lack of distinction in many studies may explain, to some degree, the conflicting results when investigating what causes 'psychosis'.

1.1.e. – Aetiology

What causes psychosis? A biopsychosocial disorder

Despite a very significant number of research projects looking at the neurobiology of psychosis, particularly schizophrenia, over the last few decades, no single factor has been directly linked with the origin of the condition. Current evidence suggests that the onset of psychosis appears to be the result of a combination of biological, psychological and social factors and complex interactions between them, which I will briefly discuss in the subsections below.

1.1.e.1. – Genetics

The greatest single risk factor for psychosis, particularly schizophrenia, is a having a close relative affected by the condition. Indeed, family, twin and adoption studies found that the prevalence of schizophrenia rises according to the degree of the affected relative up to over 40% in identical twins (Tsuang et al., 1991; Cardno et al., 1999). While this has contributed to a significant interest in identifying the so-called 'schizophrenia gene', it also suggests that other non-heritable external factors may be related to the aetiology of the disorder.

Four major findings have emerged from genetics research in psychosis. First, given that the identical twin of a schizophrenic has over 50% chance of escaping the illness, genetics does not seem to the be the whole story (Gottesman & Shields, 1982). Second, even though no one questions the genetic component of schizophrenia, no single 'schizophrenia gene' has been found. Rather, multiple individually rare mutations, each of which has a small effect size, altering genes in neurodevelopmental pathways appear to contribute to schizophrenia (Walsh

et al., 2008). Thus, up to 108 defined loci have been linked with schizophrenia (Ripke et al., 2014), which will probably increase further in the years to come. Third, Genome-Wide Association studies have confirmed the lack of specificity of genetic risk for schizophrenia with regard to bipolar affective disorder (Craddock & Owen, 2010). Finally, copy number variants, which are submicroscopic deletions and duplications of segments of deoxyribonucleic acid that are important sources of individual genomic variation through complex regulation-expression mechanisms, were found to be associated with a range of neurodevelopmental disorders such as autism spectrum disorders, intellectual disability and attention-deficit hyperactivity disorder (ADHD) (Owen et al., 2011) as well as psychosis, from which two conclusions can be drawn. First, this finding provides further support for the neurodevelopmental hypothesis of schizophrenia postulated by Weinberger (Weinberger, 1986), Murray and Lewis (Murray & Lewis, 1987) almost three decades ago. Second, consistent with Leonhard's classification of psychoses, it seems that we should view the functional psychoses as members of a group of related and overlapping syndromes that result in part from a combination of genetic and environmental effects on brain development (Owen et al., 2011).

1.1.e.2. – Neurochemistry

After the serendipitous discovery of the antipsychotic properties of chlorpromazine by Delay & Deniker in 1952 and by linking the observations that dopamine agonists could induce psychotic symptoms and that antipsychotics tended to cause Parkinson's Disease-like side-effects, Carlsson and Lindqvist formulated the so-called *dopamine hypothesis of schizophrenia* (Carlsson & Lindqvist, 1963), for which Carlsson was awarded the Nobel Prize for Medicine and Physiology in 2000.

Briefly, the dopamine hypothesis of schizophrenia implies that the illness arises from hyperactivity of the mesolimbic dopaminergic system and that the blockade of the dopamine D_2 receptor is most strongly associated with antipsychotic activity (Carlsson & Lindqvist, 1963). The role of dopamine in psychosis has also been demonstrated in at–high-risk-of-psychosis patients (Howes et al., 2011). However, the mechanism of action of clozapine, an atypical antipsychotic indicated for the management of treatment-resistant schizophrenia despite relatively weak anti-dopamine activity, suggests that other neurotransmitter systems such as serotonin may be involved in the pathophysiology of psychosis (Meltzer, 1989). Over

the last two decades additional neurotransmitters such as glutamate, GABA and acetylcholine have attracted attention from researchers as promising new pharmacological targets (Girgis & Abi-Dargham, 2012).

1.1.e.3. - Brain abnormalities

In 1976 a study using computed tomography revealed that the cerebral ventricles of patients with schizophrenia were significantly enlarged (Johnstone et al., 1976). Since these abnormalities were present in early stages of the illness, they were thought to be the result of early events of aetiological importance, i.e. neurodevelopmental problems (Murray & Lewis, 1987). Further neuroimaging research, by using MRI in patients with first-episode schizophrenia (Leung et al., 2011), confirmed these findings, which were also replicated by recent neuroimaging studies with adolescents presenting with very-early-onset psychosis (Pina-Camacho et al., 2016) and in individuals at-high-risk of psychosis (McKechanie et al., 2016). However, in contrast to the deteriorating conceptualisation of schizophrenia based on the first clinical observations made by Kraepelin, the neuroimaging changes observed in the schizophrenic brain do not appear to progress over the course of the illness, consistent with the better outcomes achieved by today's patients with psychosis (e.g. Morgan et al., 2014), which has led to speculation about '*the myth of schizophrenia as a progressive brain disease*' (see Zipursky et al., 2013).

1.1.e.4. – Early environmental factors - pregnancy and birth complications

The anatomical brain abnormalities and the neurochemical dysfunction found in patients with schizophrenia which has been described above appear to be the result of very early damage to the brain (Murray & Lewis, 1987). In keeping with this, birth weight, premature birth and perinatal hypoxia are associated with an increased risk of schizophrenia in adulthood (Cannon et al., 2002). More recent findings from neurobiology appear to provide further support for the neurodevelopmental theory of schizophrenia (Fatemi & Folsom, 2009). Moreover, paternal age, obstetric complications and cannabis use were reported to be the strongest non-genetic contributing factors to schizophrenia (Matheson et al., 2011).

1.1.e.5. – Late environmental factors - drugs use, social factors and life events

Almost half a century ago, amphetamines were reported to induce a psychotic state with some, but not all, schizophrenia symptoms (Connell, 1958). However, these patients usually achieve full remission within a relatively short period of time, even without treatment. More recently, cannabis has been strongly associated with an earlier onset of schizophrenia and poorer long-term outcomes (see Marconi et al., 2016). Specifically, an analysis with data from the Genetics and Psychosis Study, which was also used in this thesis (Chapter 4 and Chapter 6), revealed that smoking the high-potency subtype of cannabis known as *skunk*, which only has Delta-9-Tetrahydrocannabinol without cannabidiol (Potter et al., 2008), particularly at early ages, significantly increases the risk of early onset first-episode psychosis (Di Forti et al., 2009), which may explain up to 25% of psychosis cases at a population level (Di Forti et al., 2015).

In addition, the results from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, which revealed that the risk of psychosis was associated with ethnicity, being particularly increased in Black African-Caribbean people (Fearon et al., 2006), and with urbanicity (Kirkbride et al., 2008) led to proposal of a 'sociodevelopmental' model of psychosis (Morgan et al., 2010a). Furthermore, the negative impact of childhood adversity on outcomes of patients with psychosis has been the subject of a recent meta-analysis (Trotta et al., 2015).

1.1.f. – Treatment

Since the serendipitous discovery of chlorpromazine over half a century ago (Delay & Deniker, 1952), almost all antipsychotic drugs have dopamine D2 receptor (DRD2) blocking effects. Although the *first-generation antipsychotics* (FGA) successfully managed psychosis, particularly positive symptoms, the strong dopamine blockade was associated with significant side-effects such as extrapyramidal symptoms and hyperprolactinemia. The so-called *second-generation antipsychotics* (SGA), also known as *atypical,* of which clozapine is the most potent, binds and affects not only DRD2 but also other neurotransmitter receptors, such as serotonin receptors 2 (5HT-2R) (Meltzer, 1989), which is therefore a challenge to the dopamine hypothesis of schizophrenia (Carlsson & Lindqvist, 1963).

Although the SGA can be effective in the treatment of psychotic symptoms with fewer movement disorders, they carry a higher risk of cardio-metabolic side-effects than FGA (Lieberman et al., 2005). Choice of antipsychotic should be individualised and consider the patient's and carers' views (NICE, 2015). Clozapine is effective in around 60% of patients who were previously treatment refractory (Meltzer, 2013). Clozapine was also demonstrated to reduce suicide risk in patients with schizophrenia and schizoaffective disorders (Meltzer et al., 2003; Bourgeois et al., 2004). However, clinicians still hesitate about its initiation (Patel, 2012), which tends to occur 'too late' (Howes et al., 2012) because of concerns about neutropenia and practical monitoring issues.

Psychological treatments have been endorsed by the UK National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2015), which recommend that all patients with schizophrenia should be offered cognitive behavioural therapy (CBT) and family intervention in addition to antipsychotic drugs (NICE, 2015).

1.1.g. – Outcome

The term psychosis, particularly schizophrenia, is inevitably associated with a deteriorating disorder and poor outcome, which originates from the work of Kraepelin, who investigated the course of the illness in severely psychotic patients admitted to a long-term institution in Germany during the 19th century, that is, when pharmacological treatments were unavailable.

However, some clinicians today still hold this view, which may be the result of a variation of the well-known hospital (selection) bias. Thus, those patients remaining in care are those with the most severe forms of the illness, which the clinician will consider the natural outcome of the syndrome. These patients tend to receive a diagnosis of schizophrenia based on poor outcome, which is consistent with the 6-month criterion for schizophrenia in the DSM-5 (DSM-5) detailed above (Box 1.1.). On the other hand, such a diagnosis tends to be avoided in those subjects who get discharged from services (i.e., unlike a patient diagnosed with 'FEP', someone with 'schizophrenia' is less likely to get discharged from secondary mental healthcare). Hence, there is a tautological issue here with regard to the association of schizophrenia with poor outcome (for further details, see van Os et al., 2012).

An alternative approach to better understand the outcome of 'psychosis' is to follow-up all the incident cases who present with a first-episode of psychosis over a prolonged period of time (5-10 years) within a geographically defined catchment area. This approach was taken by the AESOP-10 study, which reported better long-term outcomes for FEP patients in comparison with the previous literature (Morgan et al., 2014), although the study findings may not generalise to other settings and countries.

1.1.h. – First episode of psychosis

First episode psychosis (FEP) is a clinical term used to indicate that an individual has presented with psychosis for the first time, i.e. there is no evidence of previous psychotic symptoms or treatments for psychosis. Given the above broad definition of 'psychosis', one can imagine that the concept of FEP encompasses a wide range of patients with varying presentations and diagnoses.

Over the last few decades there has been a growing interest in using FEP samples for research on psychosis. Regardless of the specific research subject (neurobiological aetiology, cognition, or outcomes, including suicide), using such a sample minimises biases associated with chronicity, such as the duration of the illness, the effects of hospitalisation or exposure to medication.

The definition of 'FEP' I used in this thesis is the experience of one or more psychotic symptoms for at least 7 days, which does not resolve by treatment within that time. These criteria are based on the WHO 10-country study (Jablensky et al., 1992) and have been previously used by our group (e.g. Kirkbride et al., 2006).

1.2. – Suicidal behaviour

1.2.a. – Concept and terms

Suicidal behaviour, which can be used interchangeably with the term 'suicidal act', encompasses both 'suicide attempts' and 'suicides', i.e. suicide completions. Most research groups use the standard suicidology nomenclature provided by O'Carroll and colleagues in their 1996 consensus paper (O'Carroll et al., 1996).

Thus, 'suicide attempt' is defined as 'a potentially self-injurious behaviour with a nonfatal outcome, for which there is evidence (either explicit or implicit) that the person intended to kill him/herself'. A suicide attempt may or may not result in injuries. 'Suicide' (completion), just suicide thereafter, was defined as 'Death from injury, poisoning, or suffocation where there is evidence (either explicit or implicit) that the injury was self-inflicted and that the decedent intended to kill him/herself' (O'Carroll et al., 1996).

In other words, 'suicidal behaviour' is defined in terms of just two core elements: self-infliction and intent. The outcome, i.e. fatal (or death) and non-fatal, distinguishes suicide

from suicide attempts, respectively. For the purposes of this thesis, I will use the broader concept of suicidal behaviour. However, while in chapter 3 I will report the findings from a sample of patients with schizophrenia spectrum disorder who took their lives, i.e. 'suicides', in chapters 4-7 I will investigate the associations of insight (and other baseline variables) with 'suicidal behaviour', i.e. including suicide attempts and suicides, in two cohorts of patients with FEP.

In the UK, in order to certify the cause of death as suicide a coroner is required to provide evidence of suicide intent 'beyond reasonable doubt'. In particular, the coroner must feel satisfied i) that the injury was *self-inflicted* (i.e. there was no evidence of any third party involvement) and ii) that the person had *intent* to die (either explicitly, i.e. a suicide note, or implicitly, for instance, the evidence provided by the last treating psychiatrist). As a result, a number of suicides are recorded as 'open verdicts' or 'undetermined cause of death' (Linsley et al., 2001). Subsequently, most suicide research groups in the UK include both categories of death when investigating suicide, which is widely accepted.

Some groups, however, support the notion of a 'suicidal spectrum' ranging from suicidal ideation to suicide completion, with decreasing prevalence and increasing lethality (Bebbington et al., 2010). Thus, although a previous suicide attempt is the strongest predictor of further suicide attempts (Sokero et al., 2005) and completed suicide (Coryell & Young, 2005), only about 10% of suicide attempters go on to take their lives (Runeson et al., 2010). Moreover, between 60% and 90% of suicide completers do not have suicidal antecedents (Isometsa & Lonnqvist, 1998). Hence, there are grounds to consider that suicide attempters and completers are different, albeit related, populations, as recently shown by Giner et al., (2013), which represents a major challenge for suicide research as explained below. However, no such differences between suicide attempters and completers were found in patients with psychosis (Innamorati et al., 2008; Giner et al., 2013). In particular, both studies directly compared suicide attempters with suicide completers in order to examine a wide range of variables which could potentially distinguish both groups, i.e. suicide attempters from completers. Interestingly, the prevalence of schizophrenia and related disorders did not differ across groups, which suggests that in patients with psychosis there is no such distinction between suicide attempters and completers. While this may be questionable, particularly in other non-psychotic psychiatric and non-psychiatric populations (de Leon et al.., 2015), it provides support for the methodology used in this thesis to investigate the role of insight in

suicidal behaviour, including suicide attempts and suicides, in patients with FEP detailed in chapters 4, 5, 6 and 7.

On the other hand, as alluded to above, worldwide suicide research leaders have recently voiced concerns about the limitation of generalising findings from suicide attempters to suicide completers, who should be considered as the 'outliers' (from a statistical point of view) of 'suicidal groups' in studies on suicide. Indeed, this may partially explain the widely recognised inability to predict risk of suicide both in clinical practice and in research (de Leon et al., 2015).

1.2.b. – Suicide in the general population: epidemiology, methods and risk factors

Every year almost one million people die from suicide around the world. In 1998, suicide constituted 1.8% of the total disease burden; this is estimated to rise to 2.4% by 2020. Specifically, 804,000 suicides were reported across the world in 2012 (WHO, 2016), which indicates an annual global age-standardized suicide rate of 11.4 per 100,000 inhabitants with significant differences between genders as follows: 15.0 for males and 8.0 for females (WHO, 2016).

In the UK, there were 106,629 suicides in the general population over 1996-2013, an average of 4,477 per year, i.e. 11.9/100,000/year. However, only between one-quarter and one-third of these individuals had been in contact with mental health services during the 12 months preceding suicide (NCISH, 2015).

Of note, suicide has become especially concerning among young people, representing one of the three leading causes of death in the most economically productive age group (15-44 years) and the second leading cause of death in 15-19 year olds (WHO, 2016), which is also the age-group at highest risk of psychosis (e.g. Palmer et al., 2005; Dutta et al., 2010).

Suicide is a public health problem in all regions of the world. However, it should be noted that 75% of suicides occur in low- and middle-income countries (WHO, 2016) where investment in research is limited (Lopez-Castroman et al., 2015a). Furthermore, in up to 23 low-income countries there are no data available on suicide at all (WHO, 2016).

Although the World Health Organization (WHO) Mental Health Action Plan 2013-2020 set up a global target of reducing the suicide rate by 10% by 2020, which is in line with a previously formulated plan from the UK Department of Health (DoH, 1999), to date only 28

countries have reported having a national suicide prevention strategy (WHO, 2016). Moreover, suicide prevention strategies have yielded mixed results so far (Hawton and van Heeringen, 2009) and suicide rates in patients under secondary mental healthcare in the UK have remained unchanged in the UK for the past five years (NCISH, 2015).

Common methods of suicide include hanging, which is the most common in the UK (NCISH, 2015), self-poisoning and jumping from a height, which vary across country and gender depending on the availability (Hawton & van Heeringen, 2009). For instance, firearms are ubiquitous in the USA and the high level of firearm ownership has been directly associated with an increased risk of firearm-related mortality (Bangalore & Messerli, 2013), including suicide (Kposowa et al., 2016). In keeping with this, reducing access to lethal methods was linked with decreased suicide rates as demonstrated by the coal-gas story in the UK in the 60s, i.e. the reduced suicide rates in the UK following the decrease in the proportion of CO in the domestic gas in the 60s, which used to be a common suicide method (Kreitman, 1976), which was also replicated later in the UK (e.g. Bennewith et al., 2007) and in other countries (e.g. Gunnell et al., 2007).

With regard to risk factors for suicide in the general population, genetic loading, personality characteristics (impulsivity, aggression), restricted foetal growth and perinatal circumstances, early traumatic life events, neurobiological disturbances, psychiatric and physical disorders, psychosocial crisis, availability of methods and exposure to models of suicide (e.g. Mann et al., 1999) have been linked with suicide (Hawton & van Heeringen, 2009). By far the strongest risk factor for suicide is a previous suicide attempt (WHO, 2016).

From a more historical perspective, suicide can be also conceptualized as a social phenomenon (Durkheim, 1897), which is supported by recent research showing an association between suicide and migration, ethnicity and social disadvantage (McKenzie et al., 2012). In keeping with Durkheim's theories, over the last century there has been an increased suicide rate in times of economic recession, including the current recession which commenced in 2007, as demonstrated by a recent systematic review, which I co-authored (Oyesanya et al., 2015).

From a psychodynamic point of view, the main contribution to understanding suicide at an individual level was made by Karl Menninger (1938). Briefly, according to psychoanalysis, suicide is the consequence of a misdirection of the instinct for survival, a turning inward of the aggressive behaviour developed for self-preservation (Menninger, 1938).

In 1999, Mann and colleagues proposed a stress-diathesis suicide model (Mann et al., 1999), which while subject to criticism (de Leon et al., 2015), is still widely accepted. Specifically, this model suggests that suicidal behaviour is the result of the effect of a stressor, including psychiatric disorders and psychosocial crises, on people with the underlying diathesis, i.e. hopelessness and impulsivity. Findings from neurobiological research appear to provide some support for this model, particularly regarding the role of serotonergic and noradrenergic systems and the ventromedial prefrontal cortex in suicide (Mann, 2003).

1.2.c. – Suicide in psychosis: epidemiology, methods and risk factors

Interestingly, in the last paragraph of his 1911 seminal work '*Dementia Praecox or the Group of schizophrenias*' Bleuler made a first comment on the very violent suicidal acts observed in patients with schizophrenia(s), who were chronically symptomatic due to the lack of effective treatments at that time:

"*The most serious of all schizophrenia symptoms is the suicidal drive*." (Bleuler, 1911). Of relevance to the following chapters of this thesis, such comment continues as follows:

"*I am even taking this opportunity to state clearly that our present-day social system demands great, and entirely inappropriate cruelty from the psychiatrist in this respect. People are being forced to continue to live a life that has become unbearable for them for valid reasons; this alone is bad enough. However, it is even worse, when life is made increasingly intolerable for these patients by using every means to subject them to constant humiliating surveillance. Most of our worst restraining measures would be unnecessary, if we were not duty-bound to preserve the patient's lives which, for them as well for doctors, are only of negative value. If all this would, at least, serve some purpose! However, like Savage, I am convinced, that in schizophrenia is this very surveillance which awakes, increases and maintains the suicidal drive. Only in exceptional cases would any of our patients commit suicide, if were permitted to do as they wished. And even if a few more killed themselves – does this reason justify the fact that we torture hundreds of patients and aggravate their disease? At the present time, we psychiatrists are burdened with the tragic responsibility to do our utmost to bring about a change in these views in the near future*" (Bleuler, 1911).

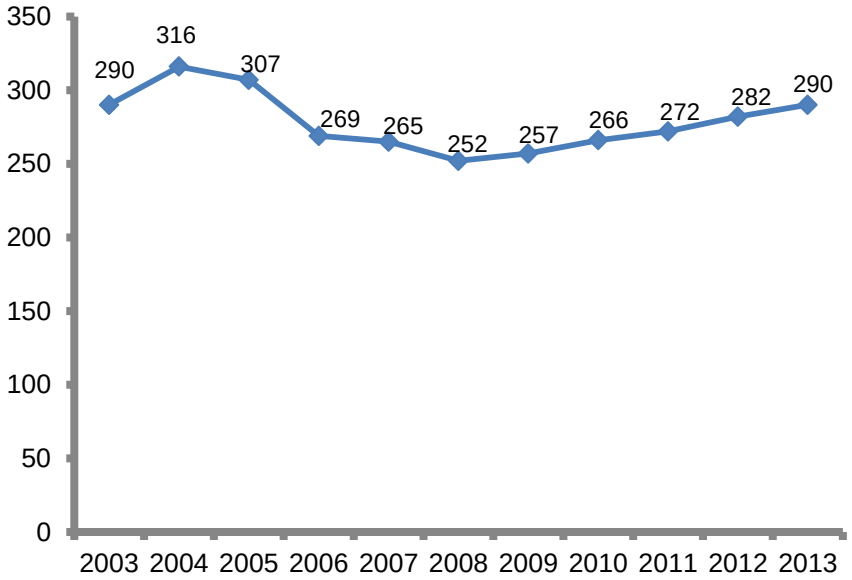
There is, indeed, a relationship between Bleuler's conceptualization of schizophrenic patients' lives, which according to him were not worth living any longer, and Camus' views of suicide (see the first paragraph of the chapter). It should be noted, however, that Bleuler's patients were pharmacologically untreated and therefore, symptomatically very unwell.

Indeed, schizophrenia and related disorders have been associated with higher mortality and shorter life expectancy than the general population (Brown, 1997), which also seems to have widened over the last few decades (Saha et al., 2007). Suicide represents a major cause of premature death among this group of patients (Brown, 1997; Saha et al., 2007; Dutta et al., 2012), with a current estimated 'lifetime risk' of 2-5% (Palmer et al., 2005; Dutta et al., 2010), which, while lower than the previously quoted estimate of 10% (Miles, 1977; Caldwell & Gottesman, 1999), remains unacceptably high. Also, following a FEP, risk of suicidal behaviour has been estimated to be up to 3% for suicide completion (SC) and 18% for suicide attempts (SA) over a 5-year follow-up period (Clarke et al., 2006).

In the light of the currently estimated lifetime suicide risk of 2-5% (Palmer et al., 2005; Dutta et al., 2010) in schizophrenia spectrum disorders in comparison to the classically quoted "10%" (Miles, 1977; Caldwell & Gottesman, 1999), one may conclude that the 'lifetime risk' of suicide in schizophrenia has decreased over the past few decades. However, the difference in these figures is because proportionate mortality (PM) is quoted, which is the percentage of the dead who died by suicide (10%) instead of case fatality (CF), which is the percentage of the original sample who died by suicide, i.e. 2-5% % (Palmer et al., 2005; Dutta et al., 2010). Since most suicides occur in early stages of the psychotic illness and all the subjects will die at some point (the later they die, the more likely they will do so from non-suicide causes), PM overestimates the real lifetime suicide risk. Similarly, CF may underestimate lifetime suicide risk since some suicides occur even two decades after first presentation with psychosis (Dutta et al., 2010). Palmer and colleagues conducted a meta-analysis of 61 studies which found CF to more accurately estimate the real lifetime risk of suicide in schizophrenia, which was reported to be 5.6% in schizophrenia (Palmer et al., 2005).

In the UK between 2003-2013, 3,066 patients (i.e. those in contact with psychiatric, drug and alcohol, child and adolescent or learning disabilities services within 12 months of their death) with a primary diagnosis of schizophrenia and related disorders died from suicide, i.e. approximately 17% of patient suicides (NCISH, 2015), which is in line with a previous meta-analysis of psychological autopsy studies (Arsenault-Lapierre et al., 2004). Of concern, in the UK there has been a steady rise in the number of suicides by patients with schizophrenia since 2008 (NCISH, 2015).

Figure 1.3. Number of suicides by patients with schizophrenia in England over 2003-2013 (NCISH, 2015)



The epidemiological evidence that suicidal behaviour is a major complication of schizophrenia spectrum disorders provides an impetus for the development of programmes for suicide prevention in this group of patients, already a core focus of mental health policies in the United Kingdom (DoH, 1999) and a priority within the World Health Organization Mental Health Action Plan 2013-2020 (WHO, 2013).

With regard to suicide method, patients with schizophrenia have been reported to frequently use violent / physical methods, particularly jumping from a height or in front of a train (Dutta et al., 2010; Nielssen et al., 2010; Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016), which was also replicated in samples of suicide attempters (e.g. Baca-Garcia et al., 2005b). This has implications for suicide prevention as restricting access to methods has been demonstrated to reduce suicide rates at a population level (Kreitman, 1976; Bennewith et al., 2007; Hawton & van Heeringen, 2009; WHO, 2016). The commonly used violent methods by patients with schizophrenia who attempt to take their lives irrespective of outcome (Baca-Garcia et al., 2005) and the lack of sociodemographic and clinical differences between suicide attempters and completers with schizophrenia and psychotic disorders (Innamorati et al., 2008; Giner et al., 2013) allowed me to analyse both groups together as detailed in the methodology sections of chapters 4, 5, 6 and 7 where further details in this respect are provided.

A meta-analysis carried out by Hawton and colleagues (2005) showed statistical significance for the following risk factors of suicide in schizophrenia: being male, white, living alone, recent loss, hopelessness, agitation/restlessness, low self-esteem, fear of mental disintegration, poor compliance, previous suicide attempt and suicidal ideation, depression, drug misuse, presence of impulsivity and a family history of depression. Reduced risk was associated with hallucinations in this meta-analysis (Hawton et al., 2005). Interestingly, no statistically significant association was found between insight and suicide which is discussed thoroughly in chapter 2. In addition, the number of previous admissions (Popovic et al., 2014), self-devaluation and insomnia (Pompili et al., 2011) were linked with suicide risk in psychosis. Interestingly, prior suicidal ideation has been found to be relatively uncommonly reported in patients with psychosis who later take their own lives (Bakst et al., 2009), which represents a real challenge in the clinical setting.

Suicide in schizophrenia and psychotic disorders usually occurs in the early stages of the disorder (e.g. Dutta et al., 2010, Lopez-Morinigo et al., 2014b; confirmed by a meta-analysis (Palmer et al., 2005)). The loss of lives in this young population and the number of years of life lost are a clear impetus for this thesis.

In keeping with this, suicide risk factors have been investigated in FEP samples, and have been the subject of two systematic reviews (Pompili et al., 2011; Challis et al., 2013; Nordentoft et al., 2015) and a meta-analysis (Challis et al., 2013). This has revealed that a history of self-harm, is associated with a fourfold increased risk, while suicidal ideation, greater insight, alcohol and substances misuse, younger age at onset and at first treatment, depressed mood and the duration of untreated psychosis all increased suicide risk to a lesser extent after first contact with mental health services.

Of note, although greater insight was associated with an increased risk of self-harm, in the 2013 Challis et al. meta-analysis of FEP studies (Challis et al., 2013), the effect size was rather small (OR=1.64, 95% CI 1.23-2.56), which was consistent with the seminal Hawton et al. meta-analysis of schizophrenia patients conducted in 2005 (Hawton et al., 2005) reporting a non-significant association (OR=2.04, 95% CI 0.54-7.74). In other words, while the above results suggest that insight may increase suicide risk in psychosis, it seems that if such an association existed, it would appear to be mediated by other variables.

1.3. – Insight

1.3.a. – History

To a large extent, the history of insight mirrors the history of psychiatry, i.e. the history of insanity, relabelled as psychosis by Ernst von Feuchterlesben in 1845 (see section 1.1.a. for further details).

Until the early nineteenth century the concept of insanity, as proposed by Hobbes and Locke, was based on the presence of delusions, which were 'insightless' by definition (see Berrios, 1996). Accordingly, physicians did not pay much attention to the, at that time, non-existent concept of insight. However, it was lawyers, who were interested in challenging 'total' insanity, who raised the issue of 'awareness of illness'; thus, resulting in the new concept of 'partial' insanity which at that time had two meanings:

- *Intermittent:* periods of madness alternated with lucid intervals. Under the current UK law, particularly in accordance with the Mental Capacity Act (MCA, 2005), this intermittent partial insanity would be, to some degree, equivalent to the current medico-legal concept of capacity as 'time'-dependent.
- *Incomplete:* madness affecting one region of the psyche, i.e. monomanias, which were defined further by the French School (Esquirol, Pinel, Falret, Baillarger) in terms of Faculty Psychology. Of relevance to the focus in my thesis, the concept of insight appeared to be first described at the same time as the definition of an 'emotional' insanity (which would be known as 'depression' in today's psychiatry). As detailed below, insight has been consistently associated with depression: the greater the insight, the lower the mood (e.g. Mintz et al., 2003). Whether insight can also lead to suicidal behaviour in patients with psychosis is a central question of this thesis.

The concept of a 'partial' madness challenged the previously unquestioned 'insightlessness', which allowed for the existence of an insanity which, to paraphrase Baillarger, 'was aware of itself' (Berrios, 1996).

In addition, this ongoing debate among the alienists in the second half of the nineteenth century incorporated new concepts into psychiatry, such as consciousness (awareness), introspection, self and subjectivity. Given that the psychological concept of consciousness was mainly understood as a form of perception, not surprisingly the term 'insight' (i.e. an inner eye) was taken to refer to the above complex concepts. According to

Berrios, the first ever clinical usage of the term 'insightlessness' dates back to 1893 by Krafft-Ebing: 'in chronic insanity, when delusions have become organized and defect has ensued, the patient is absolutely insightless to his disease' (Berrios, 1996).

In spite of the apparent link between lack of insight and psychosis, neither Kraepelin nor Bleuler paid much attention to the concept of insight, which was revived thanks to the seminal contributions made by Jaspers (1913), Lewis (1934) and Conrad (1958). Thus, Jaspers, who had suffered from a chronic pulmonary disease since his childhood, linked 'insight' to the patient's self and the knowledge of self-existence with a focus on the attitude, i.e. what is implicit (for instance, attending the relevant appointments) rather than what is explicit ('I have schizophrenia'). From the Maudsley Hospital in London, Lewis (1934) defined insight as a '*correct attitude to a morbid change in one self*' (Lewis, 1934). From a more phenomenological perspective, Conrad (1958) described the onset and progression of psychotic symptoms in patients with schizophrenia in relation to 'insight' impairment, although he did not use the term insight as such.

Finally, since the publication of a seminal paper by David in 1990 (David, 1990) there has been a growing interest in 'insight', mainly in psychosis but also in other psychiatric conditions, including the publication of two textbooks (Amador & David, 1998; Markova, 2005), one of which is in its second edition (Amador & David, 2004).

1.3.b. – Definition

The term insight only exists in English and it does not have translation into Latin languages. The *Oxford English Dictionary* provides up to three definitions of insight, the third of which applies to 'psychology':

i) Internal sight, mental vision or perception, discernment; in early use sometimes, Understanding, intelligence, wisdom.

ii) The fact of penetrating with the eyes of the understanding into the inner character or hidden nature of things; a glimpse or view beneath the surface; the faculty or power of thus seeing.

iii) ***Psychology:*** In studies of behaviour and learning, the sudden perception of the solution to a problem or difficulty; applied to animals, giving an indication of their capacity for ideas and reasoning.

The three definitions listed above link with the broader concept of insight used in the field of psychiatry. However, even a combination of the above definitions cannot capture the complexity of *understanding* i) that someone has an illness, ii) that such illness is mental and iii) the consequent attitude towards such 'mental illness', including treatment compliance.

1.3.c. – Multidimensional model of insight

In 1990 David proposed that insight is not a unitary, 'all-or-nothing' phenomenon but is composed of three different, albeit overlapping dimensions – (i) the recognition that one has a mental illness, (ii) the ability to relabel unusual mental events (such as delusions and hallucinations) as pathological, and (iii) compliance with treatment (David, 1990):

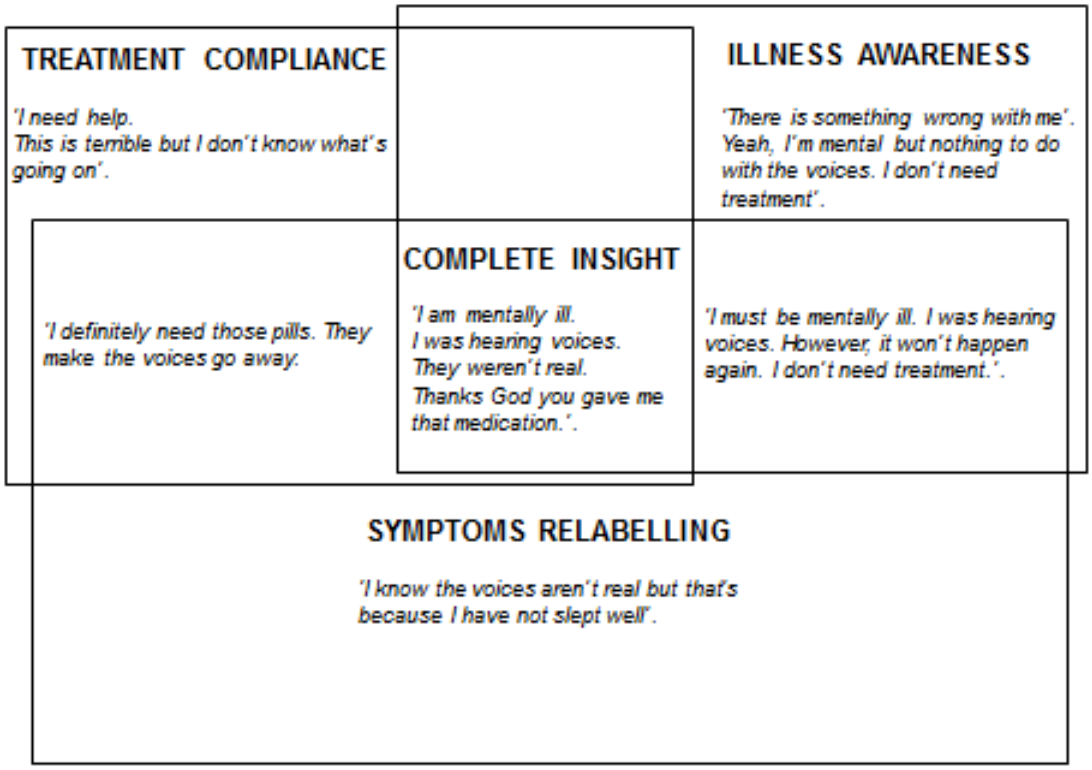
Awareness of illness – This insight dimension is not the same as accepting a label of 'psychosis' or 'schizophrenia. Rather, this factor evaluates the ability of a patient to recognise an emotional or psychological change ('something is going wrong') which appears to point to a mental illness.

Ability to recall psychotic experiences as pathological – This factor relates to the awareness of having had psychotic symptoms and the ability to attribute such psychotic symptoms to a mental illness. For instance, a patient with (stabilised) schizophrenia may recall commanding voices, yet be unable to attribute such experiences to their mental illness. This distinction between awareness and attribution was elaborated further by Amador (1991).

Awareness of the need for treatment – This insight domain is strongly associated with compliance. However, 'awareness of the need for treatment' represents a broader concept that comprises both an explicit attitude towards psychiatric treatment, including pharmacological and non-pharmacological interventions, and the implicit behaviour (for instance, how many sessions or appointments the patient fails to attend).

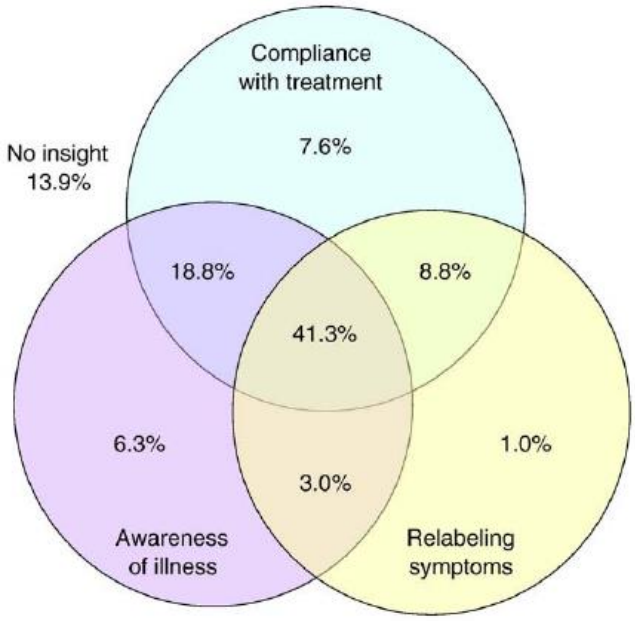
Indeed, patients present with different degrees of each insight domain, as illustrated by the clinical vignettes shown in figure 1.4 below based on David's model (1990):

Figure 1.4. Diagram showing clinical vignettes concerning the main components of insight based on David's model (David, 1990)



More specifically, while a small proportion of patients present with complete lack of insight, the vast majority of people present with 'partial' insight levels, as graphically demonstrated by this study from our group with a sample of relatively stable and well-functioning patients with schizophrenia and schizoaffective disorder who were participating in a clinical trial (Wiffen et al., 2010):

Figure 1.5. Venn diagram showing the percentage of stable patients in the early stages of schizophrenia demonstrating good levels of each dimension of insight. (taken from Wiffen et al., 2010).



1.3.d. – Insight and psychosis

So far I have discussed the concept and definition of insight 'in psychosis' because the term always refers to insight into *something*. Moreover, the object of insight may affect the concept of insight itself (Markova & Berrios, 1992).

From a historical perspective I have shown that the concept of (lack of) insight in psychosis was intrinsically linked with madness, which was relabelled as psychosis in the nineteenth century. Hence, it is not surprising that most research on insight has focused on insight in 'psychosis', particularly schizophrenia (for a review, see the aforementioned second edition of 'Insight and Psychosis' by Amador & David, 2004).

Indeed, the International Pilot Study of Schizophrenia conducted by the World Health Organization in 1973 reported that up to 97% of patients had insight deficits (Carpenter et al., 1973). Later on, with multidimensional approaches, lower prevalences of lack of insight in samples of psychotic patients were reported (e.g. Amador et al., 1994; Wiffen et al., 2010). In addition, patients with schizophrenia were found to have lower levels of insight than those with affective psychoses (Amador et al., 1994). More recently, 'poor insight' has been described as a discriminating feature of schizophrenia (Arango & Amador, 2011). The question therefore arises: what underlies lack of insight in schizophrenia and related disorders? This forms the context for section 1.3.f. below. In order to investigate the origin of impaired insight in psychosis, insight needs to be 'measured' appropriately (see section 1.3.e).

In addition to psychosis, insight into other psychiatric conditions has recently attracted interest, such as mood disorders (Ghaemi & Rosenquist, 2004), eating disorders (Konstantakopoulos et al., 2011), as well as neuropsychiatric disorders (David et al., 2012). Furthermore, about one-quarter of patients suffering from chronic physical health conditions do not take their medication as prescribed (Cramer & Rosenheck, 1998), although some authors suggest that insight into a medical illness is phenomenologically different from awareness of mental illness (e.g. Lysaker et al., 2009). Interestingly from a clinician perspective, '*we all believe that our patients have above average adherence (it's the other person's patients who have the problem)*' (David, 2010).

1.3.e. – Measuring insight

Early literature on insight in psychosis relied on patients' narrative descriptions of their beliefs around their mental illness. While this approach offers a rich view about a patient's self-assessment, it cannot be replicated for research purposes. As a result, investigators began to design interviews in which insight could be 'scored', which initially resulted in patients being classified as having 'good' or 'poor' insight. One example of this measurement of insight might be the Present State Examination (Wing et al., 1974).

Later on, semi-structured scored interviews were validated to measure insight. The first such measure was The Insight and Treatment Attitudes Questionnaire (ITAQ) developed by McEvoy and colleagues in 1989 (McEvoy et al., 1989). The ITAQ is an 11-item questionnaire which assesses patients' attitudes or beliefs about whether they have a mental illness and whether they need treatment. While an advance in the assessment of insight, this scale does not capture other domains of insight which are currently believed to constitute this complex construct. In essence, the ITAQ still measures insight from a unidimensional perspective.

Thus, in keeping with the multidimensional models of insight proposed by David (1990) and Amador (1991), two scales were validated to measure insight multidimensionally.

In 1993 Amador (Amador et al., 1993) developed the Scale to assess Unawareness of Mental Disorder (SUMD). In addition to the independent assessment of awareness and attribution, the SUMD distinguishes current and past awareness of i) having a mental disorder, ii) the effects of medication, iii) the social consequences of the illness, and iv) the specific signs and symptoms. The shortened version of the Scale to Assess Unawareness of Mental Disorder (SUMD) (Amador et al., 1994), which provides scores on three insight dimensions: insight into mental illness, insight into need for treatment, and insight into the social consequences of the illness, was used to measure insight in chapter 7 of this thesis. Of note, this scale assesses unawareness of illness, i.e. the higher the score (which ranges from 0 to 5), the poorer the insight.

The Schedule for Assessment of Insight (David, 1990), including an Expanded version (SAI-E) (Kemp & David, 1997), is an 11-item semi-structured interview easily applicable to clinical practice (Sanz et al., 1998) that provides several separate insight scores based on David's model (David, 1990): awareness of mental illness, relabelling of psychotic symptoms as abnormal and treatment compliance. A further item assessing 'hypothetical contradiction' was added to the original scale, which refers to a patients' reaction if someone were to deny

their psychotic experiences. This item was found to be part of the 'symptoms relabelling' dimension according to a factor analysis (Morgan et al., 2010b), which is also replicated in chapter 5 of this thesis. The three factors can be summed to create a total score. The SAI-E also includes items to assess compliance with medications, and a 7-point overall compliance item, to be scored by the patient's primary nurse or carer. The scale is available in appendix 5. Also, the SAI-E has been recently validated in Spanish as a result of a collaboration study, which I co-authored (Soriano-Barceló et al., 2016).

Further insight assessments commonly used in research include self-reports such as the Birchwood Insight Scale (Birchwood et al., 1994), the Markova and Berrios' Insight Scale (Markova & Berrios, 1992), which actually evaluates insight domains close to the so-called 'cognitive insight' (Beck et al., 2004), and the specific insight item of two large scales of general psychopathology such as the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987) and the Manual for the Assessment and Documentation of Psychopathology (AMDP System) (Guy & Ban, 1982).

With regard to the SAI-E, it was found to have a high correlation with both the ITAQ and, more weakly, with the Markova and Berrios's Scale, (Sanz et al., 1998), and this is detailed in table 1.3. below.

Table 1.3. Concurrent validity of SAI-E. Pearson's correlation coefficients between SAI-E and other insight scales. Taken from Sanz et al. (1998)

	ITAQ	*PANSS*	*SAI*	*M&B - a*	*M&B – b*
SAI-E	*0.845***	*0.895***	*0.97***	*0.466***	*0.410**

* p<0.05; ** p<0.01; *** p<0.001
ITAQ: Insight and Treatment Attitudes Questionnaire (McEvoy *et al.*, 1989);
PANSS: Positive And Negative Syndrome Scale (Kay et al., 1987);
SAI: Schedule for the Assessment of Insight (David, 1990);
M&B: Markova and Berrios' Insight Scale (Markova & Berrios, 1992);
SAI-E: Schedule for the Assessment of Insight, expanded version (Kemp & David, 1997).

Given the number of instruments available to measure insight, the investigator designing a study in which an insight assessment needs to be included may wonder which scale he/she should use for such a research project. In Table 1.4. below I summarise the attributes of the scales, which may be of help to guide the above decision. In particular, moving from left to right I have highlighted the advantages of a multidimensional assessment of insight.

Table 1.4. Insight dimensions assessed by scales

Dimensions of insight	PSE	PANSS	ITAQ	SUMD	SAI-E
Awareness of having a mental disorder	√	√	√	√	√
Relabelling psychotic symptoms correctly				√	√
Awareness of the social consequences				√	√
Awareness of the need for treatment				√	√

PSE: Present State Examination (Wing et al., 1994); PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987)
ITAQ: Insight and Treatment Attitude Questionnaire (McEvoy et al., 1989)
SUMD: Scale to assess Unawareness of Mental Disorder (Amador et al., 1993)
SAI-E: Schedule for Assessment of Insight, expanded version (Kemp & David, 1997)

1.3.f. – Why do patients with psychosis lack insight?

As detailed above, patients with psychotic disorders (Amador et al., 1994), particularly schizophrenia (Carpenter et al., 1973, Arango & Amador, 2011), tend to deny having a mental illness and treatment non-compliance is the rule rather than the exception (e.g. Lieberman et al., 2005). In order to explain what underlies lack of insight in psychosis, psychological (Lysaker et al., 2007), psychopathological (Cuesta & Peralta, 1994) and neuropsychological (Aleman et al., 2006) theories have been proposed.

From a psychological perspective, 'lack of insight' is viewed as having a function in terms of being protective or preserving self-esteem (Cooke et al., 2005). It is therefore intuitive to think that too much insight might be undesirable.

Cuesta & Peralta and colleagues, however, failed to link lack of insight with other psychopathological symptoms or neurocognitive deficits in different samples of patients with psychotic disorders (Cuesta & Peralta, 1994; Cuesta et al., 2000; Cuesta et al., 2011), which led them to suggesting that lack of insight in psychosis may be conceptualised as a primary symptom of the illness in a Bleulerian sense (Cuesta & Peralta, 1994).

In addition, neurocognitive deficits in psychosis in relation to impaired insight have been investigated for the last three decades (Amador et al., 1991) given the clinical similarities with so-called 'anosognosia' in neurological diseases (Babinski, 1914). The relationship between lack of insight and neurocognitive deficits was also the subject of a systematic review in 2004 (Morgan & David, 2004) and a meta-analysis encompassing 35 studies in 2006 (Aleman et al., 2006), which found a small, but significant, relationship between poor insight in psychosis and general cognition, and slightly larger with executive functions as assessed by

the Wisconsin Card Sorting Test (WCST). More recently, a study conducted by our group, which I co-authored, found verbal memory to predict insight in FEP above and beyond the effects of general cognition (i.e. intelligence quotient, IQ) (Wiffen et al., 2012). However, percentages of variance on insight dimensions explained by verbal memory (although statistically significant) were very low (Wiffen et al., 2012), in line with the results from the aforementioned meta-analysis (Aleman at al., 2006). Hence, there are grounds to consider that other variables may affect insight.

In particular, metacognition, which is defined as 'thinking about one's and others' thinking' (Frith, 1992), and particularly the so-called 'cognitive insight' (Beck et al., 2004), has recently attracted interest from research on insight, including a seminal textbook (Dimaggio & Lysaker, 2010). Interestingly, verbal memory was also associated with cognitive insight in two FEP studies (Lepage et al., 2008; Buchy et al., 2010).

In keeping with a neurological basis of insight in psychosis, a number of neuroimaging studies have investigated brain 'regions of interest'. Although results have been mixed to date (see David et al., 2012), prefrontal areas seem to emerge as the key area where complex neural circuitries, rather than specific anatomical brain regions, might underpin clinical insight in psychosis (e.g. Shad et al., 2006; Morgan et al., 2010b; Antonius et al., 2011; Bergé et al., 2011; see David et al., 2012 for a review) as well as cognitive insight (Orfei et al., 2013).

Of importance, the fourth revision (text reviewed) of the Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association in 2000 described lack of insight in patients with schizophrenia as follows (APA, 2000):

'*A majority of individuals with schizophrenia lack insight regarding the fact that they have a psychotic illness. Evidence suggests that poor insight is a manifestation of the illness itself, rather than a coping strategy. It may be comparable to the lack of awareness of neurological deficits seen in a stroke, termed anosognosia. This symptom predisposes the individual to noncompliance with treatment and has been predictive of…increased number of involuntary hospital admissions, poorer psychosocial functioning, and a poorer course of illness*' (APA, 2000).

In addition, premorbid personality (Campos et al., 2011; Cuesta et al., 2011; Ritsner & Blumenkrantz, 2007; Lysaker et al., 1999), premorbid adjustment (Ayesa-Arriola et al., 2011; Wiffen et al., 2012; Debowska et al., 1998; Keshavan et al., 2004), education level (Wiffen et al., 2010) and duration of untreated psychosis (DUP) (Ayesa-Arriola et al., 2011; Cuesta et al., 2011; Saravanan et al., 2010) have been reported to contribute to insight in FEP. Interestingly, a significant association was found between insight and psychopathology by a meta-analysis formed of 40 studies (Mintz et al., 2003), although the percentage of variance explained by symptom severity was low (less than 7%), thus suggesting that other factors may play a more relevant role in insight. While both positive and negative symptoms showed a negative relationship with insight, as expected, depression was the only psychopathological dimension that positively correlated with insight (Mintz et al., 2003), i.e. the greater the insight, the more severe the depression. A further meta-analysis of 59 studies carried out in 2015 (Belvederi et al., 2015) showed a small (effect size r=0.14-0.17), but significant, association of depression with illness awareness and symptoms relabelling. On the other hand, neither insight into the social consequences of the disorder nor insight into the need for treatment was associated with depression.

1.3.g. – Can insight be improved?

Insight has been demonstrated to be a dynamic phenomenon, which can evolve over the course of the illness, showing a tendency to improve in the first stages of psychosis (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011, Quee et al., 2011). However, 'lack of insight' has also been shown to have trait-like qualities (Wiffen et al., 2010), which led to speculation that insight may be, to some extent, determined on first presentation with psychosis (Cuesta et al., 2011). Hence, it seems that insight may have both trait- and state-like properties (Wiffen et al., 2010). However, a 3-year follow-up FEP study with the sample used in chapter 7 of this thesis revealed that lack of insight in FEP appears to behave as a trait of the illness, which may also be determined from first contact with services (Ayesa-Arriola & Lopez-Morinigo, 2014).

With regard to therapeutic interventions for lack of insight in psychotic disorders, a meta-analysis in 2013 found small non-significant effects for cognitive-behavioural therapy (CBT) and psychoeducation, although only five studies met the inclusion criteria for each of the above therapies (Pijnenborg et al., 2013). However, larger effects emerged from those studies in which a combination of different treatments, including medication, was delivered to participants (Guo et al., 2010; Fung et al., 2011). In keeping with this, a secondary analysis of data from the European First-episode Schizophrenia Trial (EUFEST) study reported treatment with antipsychotics to be associated with significant insight improvement over the first three months after which insight improvement was no longer significant (Pijnenborg et al., 2015).

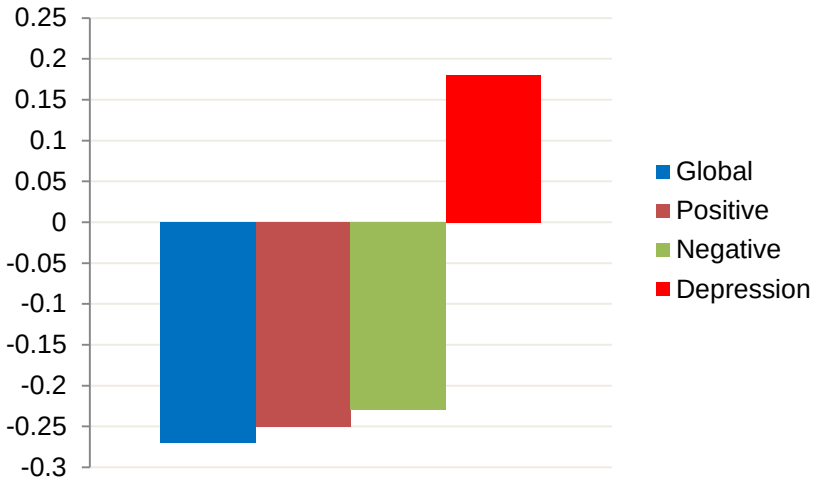
1.3.h. – Insight and clinical outcomes

Is insight always 'good'?

Insight has been consistently linked with better long-term outcomes in psychotic disorders, including improved compliance, reduced number of hospitalizations and better psychosocial functioning (e.g. David et al., 1995; McEvoy, 2004; Lincoln et al., 2007). Hence, the direction of the associations between insight and outcome appears to be positive, the greater the insight the better the outcome, which highlights the importance of further research on interventions into lack of insight in psychosis (see section 1.3.g. above).

However, an inverse association of insight with depression (better insight, worse depression) has been consistently demonstrated as shown by a meta-analysis (Mintz et al., 2003) summarised in figure 1.6. below. This so-called 'Insight Paradox' (Lysaker et al., 2007) has recently been subjected to a meta-analysis (Belvederi et al., 2015), which revealed that while recognition of mental illness and symptom relabelling were linked with depression, treatment compliance did not show such an association. Moreover, as many clinicians hold, too much insight (into such a devastating condition) may lead patients to depression, demoralization, and even suicide (Drake & Cotton, 1986), although the latter has not been confirmed yet (Restifo et al., 2009), which forms the context for the next section and the research work presented in this thesis.

Figure 1.6. Insight and psychopathology (results from Mintz et al., 2003)



1.3.i. – Criticisms of insight

Given the aforementioned relationship between insight and depression (e.g. Mintz et al., 2003) and the subsequent negative effect of insight on patients' self-esteem, even though this association appears to be much more complex (see Ghaemi & Rosenquist, 2004; and Belvederi et al., 2015 for reviews), not surprisingly insight has received much criticism since the seminal contribution made by David in 1990 (David, 1990).

Thus, this article (David, 1990) was followed by two Lancet editorials arguing '*against insight*'. The first one, with no authors listed and published in the same year (1990), compared insight with a '*full confession leading to absolution*' and insight was considered to be '*academically nourishing but clinically sterile*'. A second Lancet editorial in 1993 described insight (assessment) as a confrontation between the doctor (or therapist) and the patient (Joyce, 1993). In keeping with these views, Perkins & Moodley (1993) claimed that judging a patient as lacking insight was a form of 'Eurocentric' arrogance from doctors, that is, the only ones who know the correct way to label an illness (Perkins & Moodley, 1993). Despite such an antipsychiatry approach, it is undeniable that cultural factors such as the construction of the concept of illness, including psychosis, play a significant part in the complex concept of insight (for a review, see Kirmayer et al., 2004), as do attitudes of family members (Gigante et al., 2004). In addition, expressed emotion by carers, which is highly influenced by culture too, contributes to negative outcomes in patients with a FEP such as the so-called 'post-psychotic depression', hence suggesting the importance of family interventions, also taking into account cultural issues, early in the course of the illness (Upthegrove et al., 2013).

From a more personal perspective as researcher and clinician, it seems that the main criticism of insight in research comes from the categorisation of patients as 'lacking insight' rather than understanding each individual's view of his/her illness. Although it is true that clinical research is about investigating distributions of variables across 'groups' in relation to outcomes, current insight scales such as the SAI-E (Kemp & David, 1997) do take into account cultural aspects of the subject when rating his/her insight levels.

After this general introduction to psychosis, suicidal behaviour and insight, chapter 2 continues with a summary of previous research on the relationship between insight and suicide risk in psychosis.

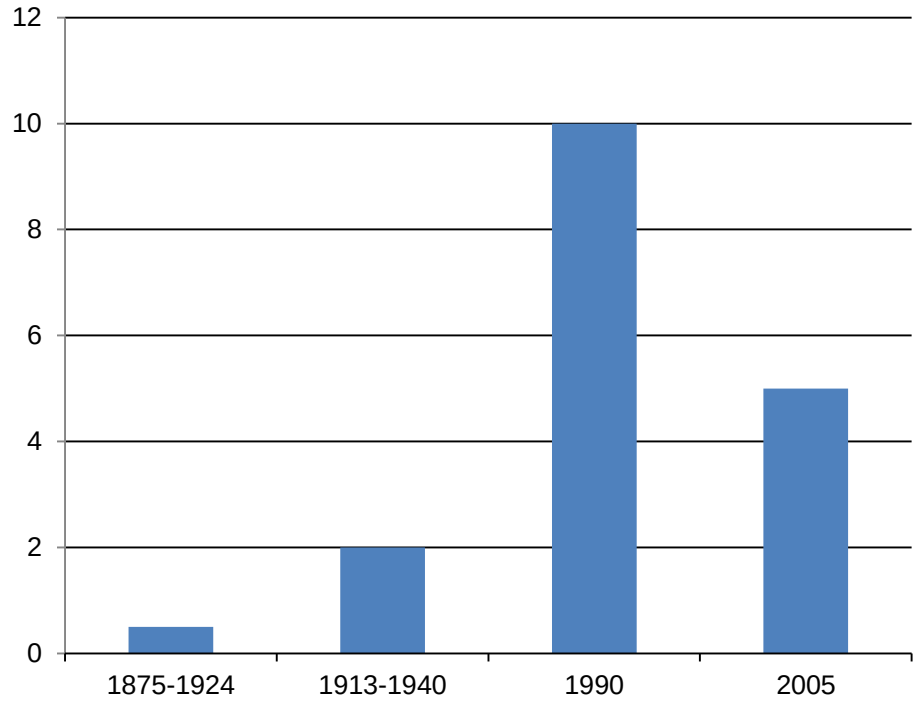
Chapter 2 – The role of insight in suicidal behaviour in psychosis: previous research

2.1. – Introduction

In 1952 the first antipsychotic, chlorpromazine was serendipitously discovered by two French psychiatrists, Delay and Deniker (Delay & Deniker, 1952). For the first time in the history of psychiatry, (positive) psychotic symptoms could be alleviated to a large extent, which significantly contributed to the 'de-institutionalisation' of patients and the commencement of community psychiatry (Thornicroft & Bebbington, 1989).

Paradoxically, such a successful change in the management of psychosis was accompanied by an increase in recorded rates of suicide in schizophrenia, from 0.5-2% in the late 19th century and early years of the 20th century (Stephens et al., 1999; Healy et al., 2006) to 5-10% over the last few decades (Caldwell & Gottesman, 1990; Palmer et al., 2005), which is illustrated in figure 2.1. below, although epidemiological research from Scandinavian countries found a decrease in suicide rates in patients with schizophrenia after deinstitutionalisation (Heilä et al., 2005; Rantanen et al., 2009).

Figure 2.1. Suicide rates in patients with schizophrenia over the 20th century



Is insight a risk or a protective factor for suicidal behaviour in early psychosis?

This subheading summarises the main research question of this investigation. In order to answer this research question, I will analyse data from three cohorts of FEP patients, which are presented in chapters 4, 5, 6 and 7 before reaching a conclusion based on all the data which is detailed in chapter 8.

The aforementioned seminal meta-analysis conducted by Hawton and colleagues in 2005 found no statistically significant association between insight and risk of suicide in schizophrenia, although the odds-ratio (OR) was 2.04 with a wide confidence interval (95%, CI 0.54-7.74), suggesting that insight may still be a risk factor (Hawton et al., 2005). A more recent meta-analysis of eight FEP studies replicated such a relationship, with an OR of 1.64 (95%CI 1.23-2.56). Indeed, it is commonly believed amongst clinicians that insight into illness in patients with schizophrenia might lead to a sense of hopelessness, demoralisation, depression and sometimes suicide, which is also supported by some research conducted in the 1980s (Drake & Cotton, 1986), although not replicated recently (Restifo et al., 2009). Nevertheless, insight has been consistently associated with low mood in schizophrenia (Mintz et al., 2003; Nair et al., 2014; Belvederi et al., 2015).

In chapter 1 (section 1.3.c.) I argued that insight is not an 'all-or-none' concept (David, 1990). Rather, a multidimensional model of insight has been consistently replicated (Amador & David, 2004). Accordingly, a first step may be to reformulate my research question as follows:

Which dimensions of insight (if any) behave as risk factors of suicidal behaviour in early psychosis and which dimensions (if any) are protective?

Interestingly, Hawton et al's meta-analysis (Hawton et al., 2005) considered insight and compliance separately and found a significant odds-ratio for poor compliance (OR=3.75 95% CI 2.20-6.37) as a risk factor for suicide, which was consistent with later studies (e.g. Lui, 2009). Hence, there are grounds to speculate that better insight might reduce suicide risk via improved compliance.

I proposed that the inconsistency of results concerning the role of insight in developing suicidal behaviours in patients with schizophrenia and related disorders as revealed by Hawton et al.'s meta-analysis may relate to: a) methodological differences between studies; b) the complexity of the concept of insight; c) assessment of insight using scales that attempt to

measure it from a unidimensional perspective; and d) the extent to which potential confounders and other possible mediating factors such as feelings of hopelessness and depression are taken into account (Lopez-Morinigo et al., 2012).

2.2. – Systematic review of previous literature

Given the above inconclusive findings with regard to my research topic, in the early stages of my PhD studies I conducted an updated systematic review of 'insight, suicide and schizophrenia' by including all the relevant articles published on PubMed up until June 2010 which resulted in a peer-reviewed publication (Lopez-Morinigo et al., 2012). Of note, this publication was followed by increased and fruitful research interest in this area, including a further systematic review focused on 'insight and suicidal behaviour' in first-episode schizophrenia (Melle & Barrett, 2012).

More specifically, since the publication of my systematic review (Lopez-Morinigo et al., 2012), two cross-sectional studies with samples of schizophrenia patients (Kao & Liu, 2011; Yan et al., 2013) and two FEP studies have reported data on the association of insight with suicidal behaviour (Upthegrove et al., 2014; Barrett et al., 2015), including a meta-analysis of 8 FEP studies with information on this subject (Challis et al., 2013). In this review I have not included a publication from our group (Ayesa-Arriola et al., 2015) since data from this study are analysed further in chapter 7. Also, there has been a growing research interest in the relationship between insight and depression both in schizophrenia (e.g. Misdrahi et al., 2014) and in FEP (e.g. Upthegrove et al., 2014), which has been subjected to a recent meta-analysis (Belvederi et al., 2015).

Thus, in order to systematically examine the role of insight in schizophrenia and risk of suicidal behaviours, initially I conducted a PubMed review of papers that assessed both insight and suicidality, in samples of patients with schizophrenia spectrum disorders during the period January 1977- June 2010, which was published in 2012 (Lopez-Morinigo et al., 2012). For this thesis, I also updated the above search in June 2016, including not only PubMed but also two further databases namely PsycInfo and Embase since papers related to my PhD topic may have been published in non-medical journals or in the 'grey' literature outside Medline.

I decided to limit the search to this period (as far back as 1977) to ensure that the studies included would be based on similar definitions of schizophrenia and related disorders such as schizoaffective disorders, i.e. only criteria from ICD-9 (WHO, 1977) and DSM-III (APA, 1980) onwards were considered valid. Thus, all the articles finally selected would be using a similar concept of schizophrenia spectrum.

The search strategy utilised 'Medical Subjects Headings' (MeSH headings) and keywords ("suicid*", "self-harm*", "schizophr*", "psychos*", "psychot*", "illness*", "insight*", "awareness*" and "consciousness*") with extensive use of cross-referencing. The only initial search limitation was by English language. This preliminary search yielded 1,193 references. The following selection criteria were applied to the abstracts:

- Sample size of more than 10 patients.
- Age: 16-65 years.
- Diagnosis: 'Schizophrenia spectrum disorders', encompassing Schizophrenia, Schizoaffective Disorder according to either ICD-9 (APA, 1977), or ICD-10 (WHO, 1993), or DSM-III (APA, 1980), DSM-III-R (APA, 1987) or DSM-IV-TR definitions (APA, 2000); or first-psychosis episode (FEP) according to the DSM-IV-TR criteria (APA, 2000).
- Insight assessments, including simple dichotomous measurements (i.e. 'absent/present') had to be included.
- Data available concerning suicide attempts (SA) and/or suicide completions (SC).
- Outpatient status of patients during the observation period (i.e. not institutionalised patients).
- In case of replication studies by the same group, only the latest one - with the largest sample size - was included.
- Although data derived from clinical trials (e.g. Bourgeois et al., 2004) was included (given the lack of evidence concerning the influence of any particular antipsychotic drug on insight), psychotherapeutic intervention studies were excluded.
- References from selected articles were also hand-searched and they were included in the review if they met the criteria above and if they were indexed into either PubMed or PsycInfo.

Initially, a meta-analysis was attempted with the data available. However, this approach was not feasible owing to the methodological differences between the studies, such as the insight assessment, the illness stage of participants, the study design (cross-sectional vs. prospective) and the lack of consistent quantitative data required for meta-analysis.

Therefore, I chose to conduct a narrative review of the selected articles, using a semi-quantitative approach.

The initial search yielded a total of 1,193 papers, namely 563 PubMed articles, 134 from PsycINFO and 496 references emerged from EMBASE. The abstracts were screened against the above selection criteria by two researchers independently (JDLM RRR, see Lopez-Morinigo et al., 2012). Thus, 20 studies were finally included in the review.

These were divided into those showing a positive association between the 'classic' insight dimension (i.e. recognition of having a mental illness) and risk of suicide: the greater the level of insight, the higher the risk of suicide (Table 2.1); and those studies that did not show such association, which meant that there was either an inconclusive association or that insight represented a protective factor: the greater the insight, the lower the risk of suicide (Table 2.2). This lack of conclusiveness with regard to such a clinically relevant potential association led me to conducting further data-based research which is presented in chapters 4-7 of this thesis.

The six positive association studies (Table 2.1) represent a total sample size of 2,606 patients. Also, three of them reported follow-up data (Crumlish et al., 2005; Gonzalez, 2008; Robinson et al., 2009), comprising 1,771 patients with a mean 1.6 year follow-up (approximately 1,825 person-years).

The fourteen negative studies, i.e. they failed to find an association of insight with suicide risk, (Table 2.2) represented a total sample size of 2,996 patients. Of note, five of them had a prospective design (Yen et al., 2002; Bourgeois et al., 2004; Acosta et al., 2009; Bakst et al., 2009; Robinson et al., 2010). These five studies comprise 1,366 patients, followed-up for a mean of 3.5 years (approximately 4,842 person-years). Of interest, 27 completed suicides were reported. Thus, a case fatality (CF) of 1.30% was estimated (27 in 1,366). A mean risk of suicide attempt (SA) over the mean follow-up period (3.54 years) was also calculated, 11.55%.

2.2.a. – Positive association studies (see Table 2.1)

Four studies with FEP patients (Crumlish et al., 2005; Foley et al., 2008; Harvey et al., 2008; Robinson et al., 2009) were identified and up to 12.6% of these patients had made a SA before the index episode.

Also, three studies had a cross-sectional design (Harvey et al., 2008; Foley et al., 2008; Schennach-Wolff et al., 2009). Colleagues from our group, who analysed a subsample of the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) cohort (presented in chapters 5 and 6), reported a significant positive association between a background of self-harm and higher scores on both overall insight and the recognition of illness, which were measured using the multidimensional SAI-E (Kemp & David, 1997), during the first presentation with psychosis, while no significant correlations between compliance and a history of self-harm were found (Harvey et al., 2008). In keeping with this, a cross-sectional FEP study from Dublin (Republic of Ireland) (Foley et al., 2008) with 107 patients found insight, which was assessed through a self-rater-based scale such as the Birchwood Insight Scale (BIS) (Birchwood et al., 1994), to be the only significant factor associated with a history of previous suicide attempts, which was present in a small group of 10 patients (9% of the sample). Assessing insight from a unidimensional approach with the insight item of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987), similar findings were reported by Schennach-Wolff and colleagues (Schennach-Wolff et al., 2009) in a sample of 339 patients with schizophrenia spectrum disorders, among whom 75 (22%) had made a SA before the index episode. At discharge, suicidal patients showed a significantly lower score on the PANSS insight item (greater insight), means: 2.0 vs. 2.4, respectively.

Among these six positive studies, only Robinson and colleagues (Robinson et al., 2009) reported data about suicide completions: six deaths by suicide recorded in their sample of 661 FEP patients, who had been followed-up over two years. A CF of 0.9% was consequently obtained. Insight was qualitatively assessed with the insight item from the Early Psychosis Prevention and Intervention Centre (EPPIC) interview (unidimensionally as absent, partial or full). Among those who made a SA over the follow-up (57 cases, 8.6%), a lower proportion had presented lack of insight (42%) at baseline compared to the non-suicidal group (64%). In this case, lack of insight at baseline appeared to show a protective effect on the development of suicidal behaviours.

In the study by Crumlish and colleagues (Crumlish et al., 2005), 101 patients with FEP were followed-up over four years during which over a third of the initial sample made at least one SA. Interestingly, insight (assessed by self-reports and the PANSS item) improved over the follow-up and its assessment at 6 months predicted a suicidal event up to four years later.

Similar findings were reported from a prospective study with a larger sample of 1,009 more chronic schizophrenia patients by Gonzalez (Gonzalez, 2008). Among the 67 patients who made a SA over the 6-month follow-up (6.6% of the sample), a high proportion of them (59, 88%) had recognized having a mental illness at baseline.

Table 2.1. Insight as an apparent risk factor for suicide

Studies	N initial	Design (if P, FU)	N at FU (%)	Age Mean ± SD	Diagnosis	Insight Scales	CF (%)	SA pFEP n (%)	SA-FU n (%)	Findings
Harvey, 2008	496	C	NA	30 ± 10	FEP, ICD-10	SAI-E	NA	56 (11.3)	NA	Previous SA associated with overall insight and illness recognition, not with compliance.
Foley, 2008	107	C	NA	30 ± 11	FEP, DSM-IV-TR	BIS	NA	10 (9)	NA	Illness recognition linked with previous SA.
Schennach, 2009	339	C	NA	34 ± 11	Sch spectrum DSM-IV	PANSS	NA	75 (22.1)	NA	Those with previous SA showed greater insight.
Crumlish, 2005	101	P (4y)	81 (80)	26 ± 8	FEP, DSM-IV-TR	IS PANSS	NA	NA	20 (19.8)	Insight improved over the FU and its assessment at 6-month FU predicted developing a SA up to 4 years later.
Robinson, 2009	661	P (2y)	658 (99)	22 ± 3	FEP, DSM-IV	EPPIC item	0.9	93 (14.3)	57 (8.7)	A lower proportion of suicide attempters over FU lacked insight at baseline.
Gonzalez, 2008	1009	P(6m)	370 (36)	42 ± 10	Schizophr ICD-9	Present/ Absent	NA	157 (15.5)	111 (11.1)	Those who made a SA over the FU, a high proportion had recognized having a mental illness at baseline.
TOTAL/MEANS	2713	1.6y	1109 (62.6)	32.85			0.9	14.9%	10.61%	

N: Sample size. n: number. P: Prospective. C: Cross-sectional. FU: Follow-up. SD: Standardized deviation CF: Case-fatality. SA: Suicide attempt. FEP: First-Episode Psychosis. pFEP: prior to FEP. ICD: International Classification of Diseases. NA: Not available (or not applicable). Sch: Schizophrenia. Schform: Schizophreniform. DSM: Diagnostic and Statistical Manual of Mental Disorders. DSM-IV-TR: Fourth Edition of DSM. y: years. SA pFEP: Number and percentage of SA prior to the FEP. SA-FU: Number and percentage of SA during the follow-up. SAI-E: Scale for Assessment of Insight, expanded version (Kemp & David, 1997). IS: Insight Scale (Birchwood et al., 1994). PANSS: Positive and Negative Syndrome Scale for schizophrenia (Kay et al., 1987). EPPIC: Early Psychosis and Intervention Centre intake mental state examination.

2.2.b. – Negative studies (see Table 2.2)

The first study to test the association between insight, conceptualized as a multidimensional phenomenon, and suicide in a sample of patients with schizophrenia was carried out by Amador and colleagues in 1996 (Amador et al., 1996). In this multicenter study, 218 schizophrenia patients were recruited (mean age: 34 years). Forty-nine of them (22.5%) had reported a SA in the past. After administering the SUMD (Amador et al., 1991), neither general awareness of having a mental disorder, nor awareness of the need for treatment nor awareness of the social consequences of the illness were significantly different between the suicidal and the non-suicidal group (bivariate analyses by Chi-square tests). A significant association between awareness of some symptoms - delusions, asociality, anhedonia and blunted affect - was found in the bivariate analysis, but these correlations were not replicated by the multivariate regression model (Amador et al., 1996).

Previously, Hu and colleagues (Hu et al., 1991) had carried out a post-mortem study with a group of 42 patients who had died by suicide and two more control groups. No significant differences in terms of presence-absence of insight were found in the comparative analyses between the cited groups (Hu et al., 1991).

Two negative studies deserve special consideration since both showed similar findings with contrasting study designs: a cross-sectional study (Kim et al., 2003) and a prospective study (Bourgeois et al., 2004). In the cross-sectional study (Kim et al., 2003) insight was assessed with the Hamilton Scale item (Hamilton, 1960) through the authors' transformation of the depression insight item in a sample of 333 schizophrenia patients with a high risk of previous suicidality (up to 60% of the sample). The multivariable regression analysis not only failed to demonstrate an association between insight and a suicidal history, but also showed hopelessness as the only factor correlating with previous suicidality. This finding was replicated in a prospective study with a larger sample size (980 patients) (Bourgeois et al., 2004). However, the sample was part of clinical trial and so while they represented a high-risk group, they were closely monitored. Indeed, only eight patients completed suicide over the 2-year follow-up, which would represent a CF of 0.81%, although nearly half the initial sample had to be hospitalized and thereby risk of exhibiting a suicidal behaviour was diminished. Interestingly, insight improved during the follow-up while risk of suicide decreased.

More recently, four cross-sectional studies failed to find any relationship between insight and risk of suicide, including three samples of patients with schizophrenia and

schizoaffective disorder (Restifo et al., 2009; Salgado et al., 2010; Yan et al., 2013) and FEP study (Barrett et al., 2010a). Thus, Restifo and colleagues (Restifo et al., 2009) had demonstrated bivariate correlations between insight (assessed as present or absent) and previous suicidal behaviour (present in over a third of their sample of 174 patients), which was no longer significant when multivariable analyses were undertaken. In line with this, despite using a multidimensional assessment of insight such as the SUMD (Salgado et al., 2010) or the ITAQ (Yan et al., 2013), no significant associations of insight with previous suicidal history emerged from the analyses. Similarly, Barrett and colleagues (Barrett et al., 2010a) did not find significant differences between the suicidal group (a quarter of the sample) and the non-suicidal group with regard to insight scores on the PANSS item.

Four other negative studies presented a longitudinal design (Yen et al., 2002; Bakst et al., 2009; Acosta et al., 2009; Robinson et al., 2010). In Taiwan, Yen and colleagues (Yen et al., 2002) reported the lack of significant associations between any of the insight dimensions, assessed from a multidimensional approach with the SAI-E (Kemp & David, 1997), and the development of suicidal events during the one-year follow-up of a sample composed of 74 patients. However, 12 patients were hospitalized and another four were lost to follow-up.

Acosta and colleagues (Acosta et al., 2009) conducted a study with 73 inpatients, 57 of whom were followed-up up one year after discharge. No significant differences were found between the suicidal group (36.9% of the initial sample) and the non-suicidal one with regard to the level of awareness of having a mental illness, which was measured with the first three items of the SUMD (Amador et al., 1993).

More recently, two longitudinal studies with samples of FEP were published (Bakst et al., 2009; Robinson et al., 2010). While Bakst and colleagues (Bakst et al., 2009) reported a percentage of SA of 12.3% (initial sample: 529 patients) over a 4-year follow up; the Robinson's group (Robinson et al., 2010) followed-up a smaller sample (413 patients) but with longer follow-up (7.4 years) and found a higher risk of SA (21.6%). In neither the bivariate analysis (Bakst et al., 2009) nor the multivariate model (Robinson et al., 2010) were correlations found between insight (assessed in both cases unidimensionally) and risk of suicide.

Interestingly, a large epidemiological study from Beijing (China) with urban schizophrenia patients (Yan et al., 2013) revealed quality of life, urbanicity and having a major medical condition to be the strongest risk factors associated with having a lifetime history of suicide attempts versus those without, while there were no between-groups differences in

terms of insight levels, measured with the ITAQ (McEvoy et al., 1989). These findings were replicated in a sample of 50 schizophrenia patients from Spain (Salgado et al., 2010) who were cross-sectionally evaluated with the SUMD (Amador et al., 1993). In keeping with this, a cross-sectional study conducted in Istanbul (Turkey) (Evren & Evren, 2004) of 60 patients with schizophrenia spectrum disorders reported bivariate associations of total insight scores, as measured by the SAI-E (Kemp & David, 1997), with lifetime suicide attempts. However, the multivariable logistic regression models failed to replicate these associations, while depression (as risk factor) and negative symptoms (as protective factor) emerged as the main variables related to suicidal antecedents. Also, in another report from Taiwan with 104 patients with schizophrenia spectrum disorders (Kao & Liu, 2011) bivariate associations were found for two insight domains, namely insight into illness and insight into need for treatment, which were measured with the Self-Appraisal of Illness Questionnaire (SAIQ) (Marks et al., 2000). However, only insight into need for treatment survived the multivariable regression models which also showed hopelessness and previous hospitalizations to be associated with a history of suicidal behavior.

In addition, a recent 1-year follow-up FEP, which did not meet the above selection criteria since 'suicidality' had been measured with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992) rather than reporting on real suicide attempts, found that those who gained insight over the 1-year follow-up had lower scores on suicidality at that point (Barrett et al., 2015).

Table 2.2. Insight as an apparent protective factor or with an inconclusive role in the risk of suicide

Studies	N initial	Design (if P, FU)	N at FU (%)	Age Mean ± SD	Diagnosis	Insight Scales	CF (%)	SA pFEP n (%)	SA-FU n (%)	Findings
Hu, 1991	42	Cases-Controls	NA	26.9 ± 6	DSM-III-R, Schizophr	Present/ Absent	NA	NA	NA	Post-mortem study of schizophrenic patients who had died by suicide. No differences on insight compared with a control group
Amador, 1996	218	C	NA	34.3 ± 11	Schizophr, DSM-III-R	SUMD	NA	49 (22.5)	NA	Awareness of some symptoms -delusions, anhedonia, asociality and blunted affect- was associated in bivariate analyses. No insight dimension survived the multivariable regression model.
Yen, 2002	74	P (1y)	69 (93)	32.9 ± 10	Schizophr, DSM-IV	SAI-E	1.35	NA	NA	None of insight dimensions associated with suicide risk over FU
Kim, 2003	333	C	NA	35.1 ± 9	Schizophr, DSM-III-R,	HAM-D	NA	200 (60.0)	NA	Multivariable regression analysis failed to demonstrate an association between insight and previous SA. Hopelessness the strongest predictor
Bourgeois, 2004	980	P (2y)	601 (61)	37.1 ± 10	Schizophr, Schizoaffec DSM-IV	SF	0.82	NA	89 (9.0)	Insight improved during the FU while risk of suicide decreased. Hopelessness was the strongest predictor of suicidality.
Evren, 2004	60	C	NA	39.2 ± 10.1	Schizohr, SCAN	SAI-E	NA	27 (45)	NA	Insight scores did not survive multivariable regression models, which found depression and negative symptoms to be related to suicidality
Bakst, 2009	529	P (4y)	357 (67)	29.2 ± 9	FEP, DSM-III-R	HAM-D	0.56	148 (28.0)	72 (13.6)	Bivariate analyses did not show insight as a predictive factor of suicidality.
Restifo, 2009	164	C	NA	37.2 ± 11	Schizophr, Schizoaff	Present/ Absent	NA	59 (36)	NA	Multivariable analyses: no correlations between insight and risk of suicide.

Barrett, 2010a	170	C	NA	27.2 ± 8	FEP, DSM-IV	PANSS item	NA	44 (25.9)	NA	No differences in insight between patients with/without previous SA.
Robinson, 2010	413	P (7.4y)	282 (68)	23.3 ± 3	FEP, DSM-III and DSM-IV	EPPIC Item	2.9	67 (16.22)	61 (21.6)	Multivariable analyses: no association between insight at baseline and suicidality over the FU.
Acosta, 2009	73	P (1y)	57 (78)	28	Schizophr, ICD-9	SUMD PANSS	4.1	27 (36.9)		None of insight dimensions was associated with a higher risk of suicide over 1-y FU. Hopelessness as the strongest predictor.
Salgado, 2010	50	C	NA	NA	Schizophr, Schizoaff, DSM-IV	SUMD	NA	NA	NA	No correlation between insight and suicide risk.
Kao & Liu, 2011	104	C	NA	40.5 ± 14.5	Schizophr, Schizoaff, DSM-IV	SAIQ	NA	51 (49)	NA	Insight into illness did not survive the multivariable models, while insight into the need for treatment was linked with lifetime suicide attempts
Yan, 2013	540	C	NA	42.8 ± 8.9	Schizophr	ITAQ	NA	65 (12)	NA	No significant differences between attempters and non-attempters in ITAQ scores
TOTAL / MEANS	3750	3.5y	1366 (66.0)	33.72			1.30	19.65%	11.55%	

N: Sample size. n: number. P: Prospective. C: Cross-sectional. FU: Follow-up. SD: Standardized deviation CF: Case-fatality. SA: Suicide attempt. FEP: First-Episode Psychosis. pFEP: prior to FEP. ICD: International Classification of Diseases. NA: Not available (or not applicable). Sch: Schizophrenia. Schform: Schizophreniform. DSM: Diagnostic and Statistical Manual of Mental Disorders. DSM-IV-TR: Fourth Edition of DSM. y: years. SA pFEP: Number and percentage of SA prior to the FEP. SA-FU: Number and percentage of SA during the follow-up. SAI-E: Scale for Assessment of Insight, expanded version (Kemp & David, 1997). . IS: Insight Scale (Birchwood et al., 1994). PANSS: Positive and Negative Syndrome Scale for schizophrenia (Kay et al., 1987). EPPIC: Early Psychosis and Intervention Centre intake mental state examination. ITAQ: Insight and Treatment Attitudes Questionnaire (McEvoy et al., 1989). SAIQ: Self-Appraisal of Illness Questionnaire (Marks et al., 2000).

2.3. – Inconsistency of the results and directions for future research

In the light of the above systematic review, four methodological issues appear to contribute to the mixed results concerning the association of insight with suicide risk in patients with schizophrenia and other psychotic disorders (Lopez-Morinigo et al., 2012).

First, an explanation for the above inconsistent results may relate to *selection bias*, to which cross-sectional studies are subject. For example, insight may have been seen to be a risk factor for suicide due to the presence of a suicide attempt in the past in patients with reasonable insight (Gonzalez, 2008; Foley et al., 2008; Harvey et al., 2008; Acosta et al., 2009; Bakst et al., 2009). However, the presence of a SA in the past actually could represent an independent variable which may influence the levels of insight at the time of assessment. In other words, a psychotic patient who had made a SA before his/her acute episode, when asked whether he/she may have a mental illness (as part of the insight assessment), may be more likely to give a positive response, in contrast to those who had not developed such behaviour. Whether the patient is attributing the SA or the psychotic symptoms to what he/she calls 'mental illness' could not be inferred from his/her response, i.e. the insight assessment, particularly if insight was assessed in a simple unidimensional or dichotomous fashion.

Second, another problem affecting cross-sectional studies is *recall bias* - where patients are relied upon to give previous instances of SA. A more insightful patient may be more likely to remember and report such episodes plus such events, which of course are likely to be distressing, and they may also be more readily recalled if the current mood state is low (Gonzalez, 2008; Foley et al., 2008; Harvey et al., 2008; Acosta et al., 2009). This also links with the aforementioned relationship between insight and depression, which indeed deserves further theoretical debate (Belvederi et al., 2015).

Third, another methodological aspect to highlight concerns the assessment of insight. Only 6 (out of 20) studies in this review (Amador et al., 1996; Yen et al., 2002; Evren & Evren, 2004; Harvey et al., 2008; Acosta et al., 2009; Salgado et al., 2010) used a validated multidimensional scale to assess insight, which encompasses both the SAI-E (Kemp & David, 1997) and the SUMD (Amador et al., 1993). One of them was positive (Harvey et al., 2008), but this was a cross-sectional study (thus subject to both selection and recall biases) and also, one of the main insight dimensions (treatment compliance) was not associated with greater suicidality. These different results, according to the scale used, seem consistent with Hawton et

al.'s meta-analysis (Hawton et al., 2005), which reported poor compliance to be a significant risk factor for suicide, whilst failing to find a robust association between insight and suicide. Therefore, it is possible that some dimensions of insight may be associated with increasing suicide risk, while others are not (Amador et al., 1996; Yen et al., 2002; Acosta et al., 2009).

Fourth, the statistical analyses need to be considered when drawing conclusions from these studies. For example, insight lost its significant association with greater risk of suicide, which had been reached by the bivariate analyses, after conducting multiple regression analysis in at least six studies (Kim et al., 2003; Bourgeois et al., 2004; Evren et al., 2004; Bakst et al., 2009; Robinson et al., 2010; Kao & Liu, 2011). Interestingly, multivariable regression analyses tended to find depression as the main contributor to suicide risk (e.g. Baskt et al., 2009; Restifo et al., 2009; Barrett et al., 2010a).

In summary, cross-sectional studies (subject to both selection and recall biases) with unidimensional scales that do not carry out multivariable analyses may have a tendency to show *false* positive associations between insight and a greater suicide risk.

Hence, further research studies examining this clinically relevant question, namely the potential link between insight and suicide risk in psychosis, need to consider the following methodological aspects. First, larger sample sizes are required since suicide attempts, and especially suicides, represent rare phenomena. Second, longer follow-up periods from the first psychotic episode are necessary in order to capture a sufficient number of suicidal events that facilitates further statistical analyses and account needs to be taken of attrition. Although methodologically challenging, insight should be reassessed over the follow-up in order to capture its dynamicity and how insight changes influence suicide risk. Third, insight should be assessed with a validated multidimensional scale such as the SAI-E (Kemp & David, 1997) and SUMD (Amador et al., 1991). These methodological issues were considered when designing this investigation (see chapters 4-7). In addition, the possibility that service structure and other study variables may modify suicide risk should be acknowledged.

2.4. – Aims of this thesis

i. To describe the demographic characteristics of those patients with schizophrenia spectrum disorder (SSD) from the South London and Maudsley NHS Foundation Trust (SLaM) presenting between 2007 and 2013 who completed suicide (chapter 3).

ii. To compare these SSD suicide completers with i) non-SSD suicide completers; and ii) non-suicide completers with SSD; in terms of demographic and clinical variables, service use-related factors, suicide methods, the Health of the Nation Outcome Scale (HoNOS) and risk assessment ratings (chapter 3).

iii. To describe the risk of suicide in two prospectively ascertained cohorts of patients (aged: 18-65 years) admitted to the SLaM wards with a FEP and followed up over a median of 7 years (chapters 4 and 5), and in the combined sample (chapter 6) ascertained in the same manner.

iv. To analyse whether particular dimensions of insight - awareness of having a mental illness, ability to relabel symptoms as pathological and treatment compliance - act as risk or protective factors for suicidal behaviours in the above FEP cohorts within the follow-up, whilst adjusting the analyses for a range of putative demographic and clinical variables that may mediate the relationship between insight domains and risk of suicide (chapters 4, 5, 6).

v. To describe the risk of suicide in a prospectively ascertained cohort of 397 FEP patients (aged: 18-65 years) from Santander (Spain) and followed-up over 3 years (chapter 7).

vi. To analyse whether particular dimensions of insight - awareness of having a mental illness, awareness of the social consequences of the illness and treatment compliance - act as risk or protective factors for suicidal behaviours within the follow-up, whilst adjusting the analyses for a range of putative demographic and clinical variables that may mediate the relationship between insight domains and risk of suicide (chapter 7).

vii. To cross-compare the findings from these two cohorts of FEP patients, including a comparison with previous literature, in order to determine the role of insight in the risk of suicidal behaviours in early psychosis (chapter 8).

2.5. – Hypotheses

Based on the above review of previous literature and my own clinical experience, with regard to the role of insight dimensions in risk of suicidal behaviour after first presentation with psychosis, generally speaking I hypothesised that there will be differences amongst the different domains. In particular, I postulated that:

Hypothesis 1 (H1): Recognition of mental illness increases risk.

Hypothesis 2 (H2): Symptom relabeling is linked with greater risk.

Hypothesis 3 (H3): Awareness of the social consequences of the illness is associated with increased risk.

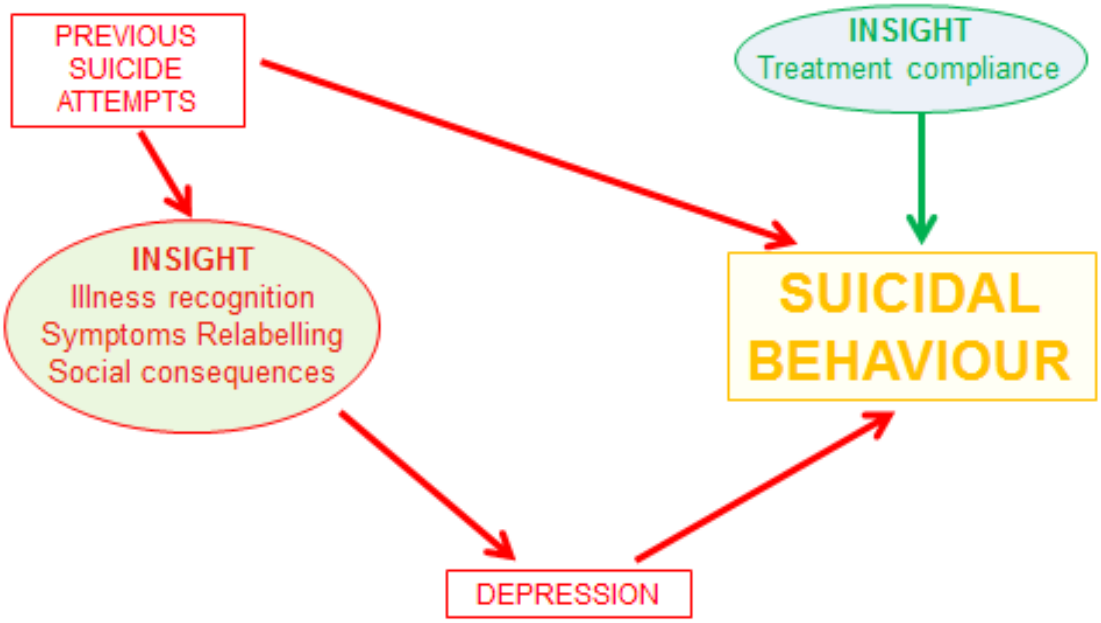
Hypothesis 4 (H4): However, regarding hypotheses 1, 2 and 3 above, the relationships between the above insight dimensions and risk of suicidal behaviour in psychosis will be confounded by depression and previous suicide attempts, both of which will be linked with both insight levels at first presentation with psychosis and suicidal behaviour risk over the follow-up periods.

Hypothesis 5 (H5): Awareness of need for treatment will (directly) reduce suicide risk.

Hypothesis 6 (H6): Overall insight will not be significantly associated with increased (or decreased) risk of suicidal behaviour.

Figure 2.2. Hypothesised model to be tested in this thesis

Red arrows indicate risk factors and green arrows indicate protective factors.



Chapter 3 – Suicide completion by patients with schizophrenia in secondary mental healthcare. Data from the South London and Maudsley (SLaM) Biomedical Research Centre (BRC) Case Register

3.1. – Introduction

This chapter describes the epidemiology of suicide completion in patients with schizophrenia spectrum disorders (SSD) who received care under secondary mental health services from the South London and Maudsley NHS Foundation Trust.

I identified a population of secondary mental healthcare users who completed suicide over the study period (2007-2013) from the SLaM case register, which is linked to national mortality data.

First, I conducted a comparison study in order to investigate demographic and clinical differences, including service use-related factors and the Health of the Nation Outcome Scale (HoNOS) (Wing et al., 1994) and risk assessment ratings, between those patients with and without SSD receiving secondary mental healthcare who completed suicide (Lopez-Morinigo et al., 2014b).

Second, I carried out a case-control study aimed to examine specific risk factors for suicide in patients with SSD (Lopez-Morinigo et al., 2016). Specifically, I compared those subjects with SSD who completed suicide, i.e. 'cases', with a group of unmatched 'controls', i.e. individuals with SSD drawn from the same register who did not end their lives in this way. In addition, I tested whether there was a relationship between disengagement, which is linked to lack of insight (Amador & David, 2004), and risk of suicide completion.

3.2. – Background

As detailed in chapter 1, suicide is a serious international public health problem. Every year almost one million people die by suicide around the world (WHO, 2014). Of note, suicide has become especially concerning among young people as one of the three leading causes of death in the most economically productive age group (15-44 years) and the second leading cause of death in 15-19 year olds (Patton et al., 2009). Since 2008, suicide prevention has become a major priority within the World Health Organization mental health policies (WHO, 2008). However, suicide prevention strategies have yielded mixed results so far (Hawton & van Heeringen, 2009). Moreover, suicide rates in the UK have remained unchanged over the past five years (NCISH, 2015).

Recent literature on suicide seems to support a 'suicidal spectrum' ranging from suicidal ideation to suicide completion, with decreasing prevalence and increasing lethality (Bebbington et al., 2010). However, suicide attempters and suicide completers appear to be two different, although overlapping, populations (Innamorati et al., 2008; Giner et al., 2013). Nevertheless, these differences between suicide attempters and completers have not been replicated in patients with SSD (Innamorati et al., 2008; Giner et al. 2013).

With regard to suicide completion, psychological autopsy studies have revealed that about 90% of people who killed themselves had a 'psychiatric disorder' (Arsenault-Lapierre et al., 2004), contributing to 47-74% of the population risk of suicide, with half of suicide completers meeting criteria for depression (Cavanagh et al., 2003; Hawton et al., 2003). Therefore, the presence of a psychiatric condition appears to be the strongest known risk factor for suicide (Cavanagh et al., 2003). It could therefore be envisaged that better management of mental disorders might reduce suicide rates. More specifically, secondary mental health services may play a crucial role in 'suicide prevention' (WHO, 2013).

While a list of risk factors have been strongly associated with 'suicidal behaviour', it remains unclear the extent to which 'known' risk factors vary across psychiatric diagnoses (Arsenault-Lapierre et al., 2004). In particular, a better understanding of associations between risk factors and diagnoses may lead to the development and implementation of diagnosis-driven suicide prevention strategies in secondary mental health services (Lopez-Morinigo et al., 2014b). For instance, limiting access to suicide methods has been demonstrated to reduce suicide rates at a population level (e.g. Kreitman, 1976; Bennewith et al., 2007). However, it

remains unclear whether there are specific associations of psychiatric diagnoses with suicide completion methods (Nielssen et al., 2010).

Suicide has been found to be the largest single cause of excess mortality in schizophrenia (Brown, 1997; Saha et al., 2007), particularly in early psychosis (Dutta el al., 2010). However, the rate of suicide in schizophrenia has been recently reported to be lower, from 2% (Dutta et al., 2010) to 5% (Palmer et al., 2005), than the previously quoted figure of 10% (Miles, 1977; Caldwell & Gottesman, 1990).

While some recognised general suicide risk factors have been replicated in schizophrenia patients such as being male, living alone and hopelessness; specific suicide risk factors, such as lower treatment adherence, have also been linked to schizophrenia (Hawton et al., 2005). Patients with schizophrenia tend not to report suicidal ideation (Bakst et al., 2009), which is a common suicide risk factor for most other psychiatric conditions (Hawton & van Heeringen, 2009). Also, suicide risk assessment in schizophrenia remains under-utilized (Pedersen et al., 2014). It therefore seems that the classic suicide prevention model has been less helpful in schizophrenia spectrum disorders than in other diagnoses. Specific suicide completion characteristics in patients with schizophrenia and related disorders in comparison to other diagnoses have not been investigated fully.

Over the last two decades the UK Department of Health has aimed to reduce suicides at a national level (DoH, 1984). In keeping with this, structured clinical risk assessments were strongly recommended by the UK NICE guidelines in 2004 (NICE, 2004) and widely used. However, more recent reviews of the NICE guidelines have voiced concerns about the limited role of risk assessment tools and scales in the clinical management of the patients (NICE, 2011). Moreover, a recent meta-analysis showed that risk scales are of little use for predicting repeat self-harm in suicide attempters (Quinlivan et al., 2016). However, the extent to which these instruments can predict suicide risk in patients with schizophrenia spectrum disorders (SSD) receiving secondary mental healthcare has not been sufficiently examined (Pedersen et al., 2014). Moreover, concerns have been voiced regarding the role of risk assessment in preventing suicide in patients with schizophrenia (Large & Ryan, 2014). Also, it remains poorly understood what specific factors evaluated by the risk assessment lead patients with schizphrenia under the care of mental health services to take their own lives.

First, I aimed to investigate differences across diagnoses (SSD vs. non-SSD) in a sample of patients receiving secondary mental healthcare from teams supervised by Consultant

Psychiatrists (i.e. not those treated solely by general practitioners (family physicians) in primary care) in South-East London who went on to die from suicide. Sociodemographic and clinical variables, including HoNOS and 'risk assessment' ratings and 'service use'-related factors, and suicide methods were compared between patients with and without schizophrenia spectrum disorders (SSD) who all died by suicide. I am the principal author of a peer-reviewed paper summarising the findings (Lopez-Morinigo et al., 2014b).

Second, I investigated potential predictors of suicide completion in patients with SSD receiving secondary mental healthcare. Sociodemographic and clinical variables, including HoNOS and 'risk assessment' ratings and 'service use'-related factors, were compared between patients with SSD who died by suicide and unmatched controls drawn from the same case register, i.e. subjects with SSD who did not complete suicide in the same time frame. Specifically, I tested whether early first contact with services, being male, white, single and unemployed, living alone, depression and related variables, particularly hopelessness and suicidal ideation, and suicidal history are associated with increased risk of suicide completion in patients with SSD under secondary mental healthcare. Also, I postulated that engagement with services, which is associated with insight (Amador & David, 2004), would reduce suicide risk in patients with SSD under secondary mental healthcare, in keeping with the fifth hypothesis of this PhD research project (H5) listed in chapter 2 (section 2.5.). This analysis resulted in a further peer-reviewed publication of which I am the principal author (Lopez-Morinigo et al., 2016).

3.3. – Aims and objectives

3.3.a. – Descriptive aims and objectives

- To describe the demographic characteristics of those patients with schizophrenia spectrum disorder (SSD) presenting between 2007 and 2013 who completed suicide.
- To compare patients with/without SSD who took their lives.
- To compare methods of suicide across groups and describe unascertainable causes of death.
- To compare patients with SSD who died from suicide with those who did not.

3.3.b. – Analytical aims and objectives

- To calculate differences in demographic and clinical variables, including the Health of the Nation Outcome Scale (HoNOS) and risk assessment ratings, between patients with and without SSD who took their lives.
- To calculate differences in suicide methods across suicide completers with/without SSD.
- To calculate differences in demographic and clinical variables, including HoNOS and risk assessment ratings, between patients with SSD who completed suicide and those with SSD who did not.
- To investigate independent risk factors for suicide. Specifically, to assess the inter-relationships between factors associated with suicide completion.

3.4. – Methods

3.4.a – Sample information

The sample comes from the South London and Maudsley (SLaM) Biomedical Research Centre (BRC) Case Register. SLaM is an NHS Trust which provides secondary mental health care to four boroughs in South-East London (UK): Lambeth, Southwark, Lewisham and Croydon. Approximately 1.23 million inhabitants reside in this geographic catchment area, which as a whole was found to be comparable with other populations of London in terms of age, gender, education and socio-economic status distributions (Stewart et al., 2009; Perera et al., 2016).

Fully-electronic health records have been in use across all SLaM services since 2006, and in 2007-08 the Clinical Record Interactive Search (CRIS) system was built which renders de-identified copies of these available for research use with appropriate governance structures (Stewart et al., 2009). Under UK law, anonymised data can be analysed without prior consent, and CRIS has received ethical approval in this respect as a data resource for secondary analyses from the Oxfordshire Research Ethics Committee C (reference: 08/H0606/71+5) (see appendix 1) currently accessing data on over 250,000 patients.

This Research Ethics approval also covers the pseudonymised linkage between CRIS data and those from the Office for National Statistics (ONS) in January 2014 (ONS, 2014), which registers all deaths in the UK and the official cause of death, including suicide and the method of suicide according to ICD-10 classification (ICD-10).

In particular, those patients who were 'active' to SLaM (i.e. had at least one face-to-face contact with a clinical member of staff) before 31st December 2013 and had died by suicide (according to the death certificate details obtained from ONS (ONS, 2014)) over the period from 1st January 2007 to 31st December 2013 were included. Those with an 'undetermined cause of death' (ICD-10 Y codes) (ICD-10) were included in the suicide group because in the UK most 'open verdicts' are very likely to be deaths by suicide since the coroner, who under UK law certifies the official cause of death, is required to provide evidence of suicide intent 'beyond reasonable doubt' (Linsley et al., 2001).

In addition, for the case-control study I selected those suicide completers with a primary diagnosis of schizophrenia spectrum disorders (ICD-10 codes F2). Five 'controls' were selected per 'case', although this was not a randomisation algorithm. Thus, for each patient

who completed suicide the five individuals with a primary diagnosis of SSD who were assessed by a SLaM member of the staff after the date of first contact with services of the index case were taken from SLaM BRC CRIS. The controls were unmatched for demographic or clinical variables to allow investigation of between-groups differences.

3.4.b. – Measures

3.4.b.1. – Demographic and clinical variables

Date of birth, gender, ethnicity, and marital and employment status are compulsory fields in the source clinical records system and were analysed.

Social deprivation was estimated with the 'Index of Multiple Deprivation' (IMD). In particular, area-level deprivation scores were available through an anonymous link created in CRIS between lower super output area residence code of the latest permanent address (a geographic unit comprising approximately 400 households) and summary data for that area from 2001 UK Census output. The Index of Multiple Deprivation is derived from seven domains: income, employment, health, education, housing and services, crime and environment (ONS, 2007).

In addition, the type of the last antipsychotic recorded (classic oral, atypical oral, clozapine, depot) and use of antidepressants (yes/no) over the study period were analysed.

Also, patient legal status under the UK Mental Health Act 1983 (Amended 2007) (DoH, 2008) was considered. I investigated whether being subject to a 'Community Treatment Order' (CTO) (DoH, 2008) was associated with risk of suicide completion in patients with SSD.

3.4.b.2. – Diagnosis

ICD-10 diagnoses (WHO, 1993) were made by the treating consultant psychiatrist. As a result, those patients who were just seen on one occasion such as a single presentation to A&E or one outpatient appointment were more likely not to be diagnosed as reported below. For analyses described in the first section of results, categories were hierarchically created from ICD-10 codes (WHO, 1993). Thus, only one of the following exclusive diagnostic categories were recorded if the patient had received more than one ICD-10 primary diagnosis: 'F2' – 'schizophrenia spectrum disorder' (SSD); 'F31 and F32.3' – 'Affective Psychosis'; 'F32.1, F32.2,

F33, F34 and F4' – 'Mood disorder/Neuroses'; 'F0 and F1' – 'Organic/Drugs'; 'F5, F6 and the remaining categories' were grouped as 'All other diagnoses'. Other patients were labelled as 'Diagnosis Unknown' because they either had a F99 or Z71.1 ICD-10 diagnosis or no diagnosis was recorded. Patients with two or more ICD-10 (WHO, 1993) primary diagnoses over time were included in only one of the above categories according to a diagnostic hierarchy. For instance, a patient with two primary ICD-10 diagnoses such as F2 and F0 was classified as SSD. Whilst many patients with SSD have other comorbidities such as cannabis misuse (e.g. Morgan et al., 2010a), given the higher stability of schizophrenia diagnosis over time (Bromet et al., 2005), we chose this category as the first in our hierarchical system. This allowed me to create two clinically meaningful categories to compare: those patients with SSD and those with non-SSD.

3.4.b.3. – Cause of death, suicide ascertainment and suicide method

Suicide method was ascertained from that recorded in the ONS Certificate of Death (ONS, 2014). ICD-10 codes (WHO, 1993) of the official cause of death (ONS, 2014) and the following groups were considered: poisoning – X64; hanging – X70; drowning - X71; cutting - X78; jumping (either from high place or in front of a vehicle) - X80, X81; suicide by unspecified means – X84; and undetermined cause of death – Y10-34.

Of note, there were also deaths from natural causes in the control group. ICD-10 codes of cause of death were recorded and nine categories were created as follows: i) neoplasms (C259-900); ii) diseases of the endocrine system (E141-149); iii) organic mental disorders (F03-09); iv) diseases of the nervous system (G060-409); v) diseases of the circulatory system (I119-850); vi) diseases of the respiratory system (J180-459); vii) diseases of the digestive system (K709-859); viii) diseases of the genitourinary system (N390); and ix) other ill-defined and unspecified causes of mortality (R99).

3.4.b.4. – Health of the Nation Outcome Scale (HoNOS)

The Health of the Nation Outcome Scale (HoNOS) has been a widely used outcome measure in British mental health services since its introduction in the 1990s. It has been reported to be a reliable and valid instrument to assess clinical outcomes, and to have easy applicability to clinical settings (Wing et al., 1994). HoNOS is formed of 12 items which assess psychopathological symptoms, alcohol/drugs use, cognitive performance and social needs. Each item is scored on a Likert scale from 0 (absent) to 4 (maximum severity), and the 12 scores are summed to create total scores, i.e. the higher the score, the more complex/severe the case. The last HoNOS score recorded was used for this study.

3.4.b.5. – Risk assessment

'Full risk assessment' is a compulsory target across the Trust when 'high risk' is deemed from a 'brief risk assessment', which is mandatory for all active cases. All patients who have been seen on at least one occasion by a member of the staff have a 'brief risk assessment' documented, which is a narrative record of the patient's risk: i) to self; ii) to others and iii) from others. If the patient is deemed at 'high' risk in any of these domains, a 'full risk assessment' needs to be completed, which consists of a structured assessment taking the form of present/absent tick-boxes enquiring about widely recognised risk factors for three major clusters: suicide, violence and self-neglect. For this study, only suicide risk assessment was taken into account, which is composed of 15 items. Positive responses can be summed to create total scores, i.e. the higher the score the greater the suicide risk (Wu et al., 2012). The most recent full risk assessment was considered for these analyses.

3.4.c. – Statistical analysis

First, distributions of continuous variables were inspected by histograms and parametric and non-parametric tests were used in order to examine differences across the above 'diagnostic categories' with regard to demographic and clinical variables. Post-hoc analyses investigated inter-groups differences. This analysis was also conducted to compare those patients with SSD who died from suicide with: i) those non-SSD patients who ended their lives; and ii) those patients with SSD who did not take their lives (i.e. 'controls' in both analyses).

People dying from suicide with/without SSD were compared in the following respects: i) on demographic and clinical variables using student t tests, Mann-Whitney U tests and Chi-square tests, as appropriate; ii) on suicide methods, calculating odds ratios and adjusting for age at the time of death and ethnicity; iii) on HoNOS, where completed, both individual HoNOS item (Mann-Whitney-U) and total scores (student t-test); iv) on full risk assessment ratings (Chi-square tests were used for individual items and t-test compared total scores across groups). Again, those subjects with SSD who took their lives were compared with the two control groups in the above respects.

In addition, receiver operating characteristic (ROC) curves (Hanley & McNeil, 1982) were plotted to assess the performance, namely sensitivity and specificity, of risk assessment total scores to predict suicide in patients with SSD. Also, the prevalence of suicide in schizophrenia (5%) (Palmer et al., 2005) was used to estimate the positive and negative predictive values.

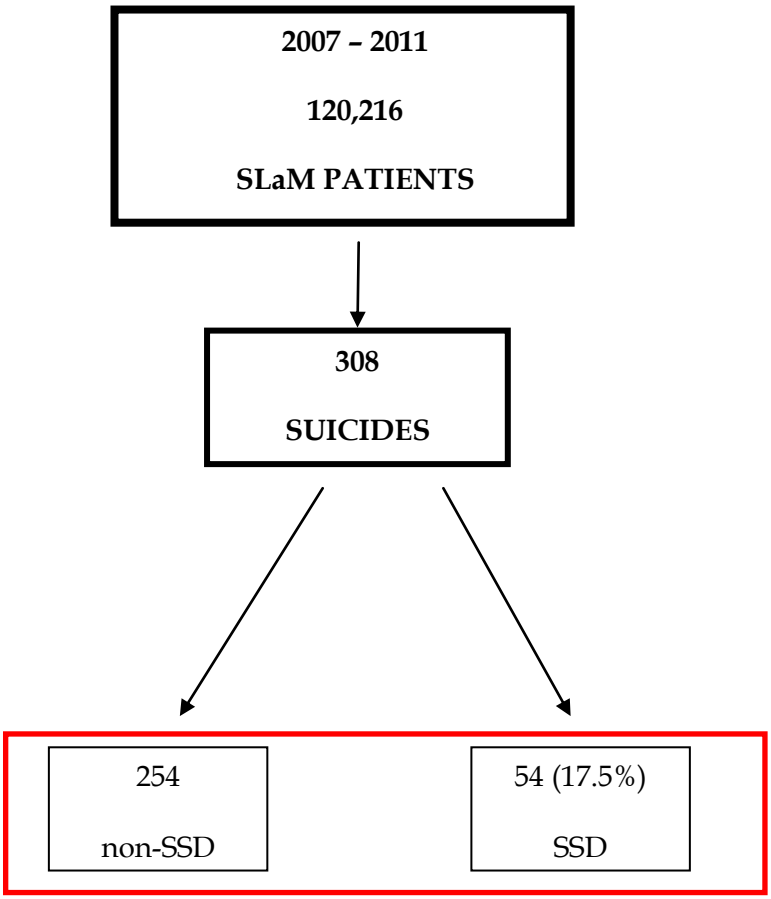
Finally, binary logistic regression models were built to investigate predictors of suicide completion. Those statistically significant variables from the above univariate analyses concerning 'cases and controls' were added to a first binary logistic regression model. A final regression model was conducted with the independent variables that remained significant. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were calculated. Specifically, the percentage of variance on the dependent variable (i.e. suicide completion) explained by each model (through the Nagelkerke R^2), the percentage of individuals correctly classified across groups (suicide completers and non-suicide completers) and the individual contribution of each independent variable to the model (ORs, 95%CIs) were investigated.

All analyses were conducted using SPSS version 22.0 (SPSS Inc, Chicago, Il, USA).

3.5. – Results

Of 120,216 SLaM 'active' service users until the 31st December 2011, 308 who died by suicide over 2007-2011 were identified from the SLaM BRC CRIS and 54 subjects with SSD (17.5%) died from suicide over the period 2007-2011, who were compared with 254 non-SSD patients who took their life over that period. See figure 3.1 below.

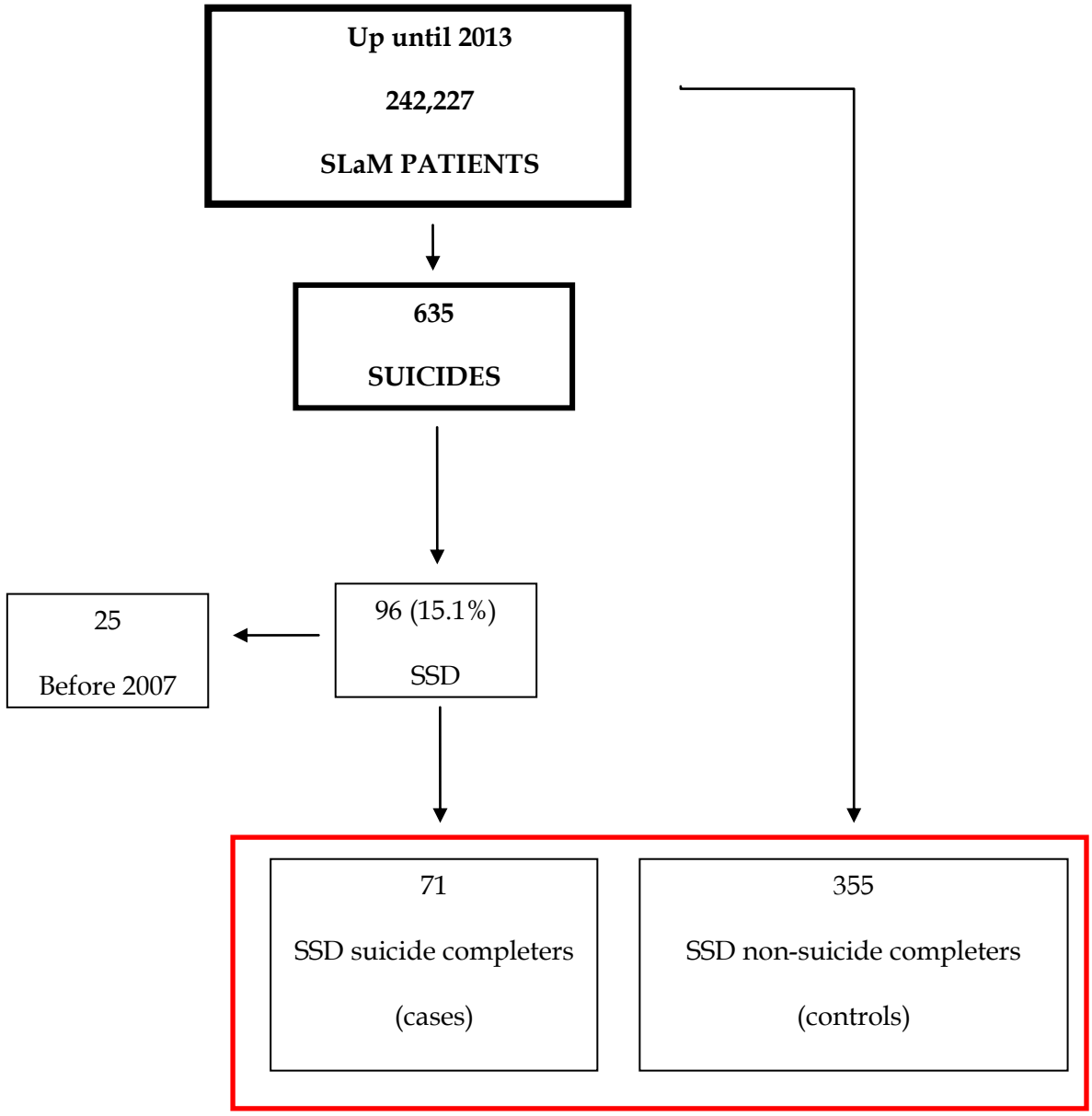
Figure 3.1. Flow chart of CRIS patients. Comparison study between suicide completers with/without SSD



SSD: Schizophrenia spectrum disorder

Of 242,227 SLaM 'active' service users until 31st December 2013, 635 suicides were identified from the SLaM BRC CRIS. Of these individuals, 96 patients (15.1%) had a schizophrenia spectrum disorder (F2-ICD10) diagnosis. Those who died before 1st January 2007 (n=25) were removed from the analyses since full electronic records before 2007 were unavailable. Therefore, 71 individuals with SSD who took their lives over 2007-2013 were compared with 355 subjects with SSD without this outcome (controls) from the SLaM BRC CRIS. See figure 3.2. below.

Figure 3.2. Flow chart of CRIS patients until 2013. Case-control study between suicide completers with SSD (cases) and patients with SSD who did not die from suicide (controls)



SSD: Schizophrenia spectrum disorder

3.5.a. – Comparison study of suicide completers: SSD vs. non-SSD

3.5.a.1. – Sociodemographic and clinical characteristics

Sociodemographic and clinical characteristics are compared between those with and without SSD in Table 3.1. No diagnostic differences were observed in gender; however, age at the time of suicide was younger in those with SSD than the remainder. There were significant group differences in ethnicity across suicide completers' diagnoses with Black ethnicity more frequent in patients presenting with SSD. IMD scores were higher in SSD compared to the remainder.

Of note, SSD cases had received longer duration of care from the Trust teams (1294 vs. 81 days) and had been seen by a member of the staff substantially more recently before the suicide event (10 vs. 146 days).

Table 3.1. Demographics, clinical and service use-related factors: SSD vs. non-SSD suicide completers

	Total sample N=308	SSD N=54 (17.5%)	non-SSD 254 (82.5%)	OR (95% CI)	p-value
		Means ± SD			
Age at death	**42.7 ± 14.0**	**39.3 ± 11.9**	**43.5 ± 14.4**		**0.04**
Deprivation (IMD)	**28.0 ± 13.7**	**32.1 ± 11.4**	**27.1 ± 14.0**		**0.01**
		N (%)			
Gender (males)	211 (68.5)	38 (70.3)	173 (68.1)	1.11 (0.58-2.11)	0.87
Ethnicity					
White	**187 (60.7)**	**26 (48.4)**	**161 (63.4)**	**0.54 (0.30-0.97)**	**0.04**
Black	**36 (11.7)**	**20 (37.0)**	**16 (6.3)**	**8.75 (4.14-18.5)**	**<0.01**
Others	**85 (27.6)**	**8 (14.8)**	**77 (30.3)**	**0.40 (0.18-0.88)**	**0.02**
First language English	**147 (47.7)**	**34 (62.9)**	**113 (44.5)**	**2.12 (1.15-3.88)**	**0.01**
		Medians (days)			
Length of service contact	**184**	**1294**	**81**		**<0.01**
Last face-to-face to death	**70**	**10**	**146**		**<0.01**

SSD: schizophrenia spectrum disorder. OR: Odds Ratio. CI: Confidence Interval. SD: Standard deviation. IMD: Index of Multiple Deprivation (ONS, 2007)

3.5.a.2. – Suicide method

As shown in Table 3.2., 'hanging' was the most common suicide method in the sample overall (131, 42.5%). SSD suicide cases had more frequently utilized 'jumping', while 'hanging' was significantly more frequent among the remainder. There were no suicides by firearms.

Table 3.2. Suicide method: schizophrenia spectrum disorder (SSD) vs. non-SSD

Method	**Total sample N=308**	**SSD n=54 54/308=17.5%**	**non-SSD n=254 254/308=82.5%**	**ORs (95% CIs)**	**p-value**
Hanging	**131 (25.9)**	**14 (25.9)**	**117 (46.0)**	**0.4 (0.2-0.7)**	**<0.01**
Poisoning	66 (21.4)	7 (12.9)	59 (23.2)	0.5 (0.2-1.1)	0.09
Jumping	**56 (18.2)**	**17 (31.5)**	**39 (15.3)**	**2.5 (1.3-4.9)**	**<0.01**
Cutting	9 (2.9)	2 (3.7)	7 (2.7)	1.4 (0.3-6.7)	0.71
Burning	3 (0.9)	2 (3.7)	1 (0.4)	9.7 (0.9-109.4)	0.08
Drowning	21 (6.8)	5 (9.2)	16 (6.3)	1.5 (0.5-4.4)	0.43
Undetermined	22 (7.4)	7 (12.9)	15 (5.9)	2.4 (0.9-6.1)	0.09

SSD: schizophrenia spectrum disorder. OR: Odds Ratio. CI: Confidence Interval

3.5.a.3. – Health of the Nation Outcome Scale (HoNOS)

116 suicide completers (37.6%) had at least one HoNOS completed. Completion rates differed across diagnoses: 83.3% of those with SSD; 35.0% of the remainder (OR=12.9, 95%CI 6.0-27.7, p<0.001). On individual items, patients with SSD scored significantly higher on 'hallucinations & delusions', while subjects with non-SSD had higher scores on 'depressed mood' and 'self-injury' (Table 3.3).

Table 3.3. Health of the Nation Outcome Scale (HoNOS): Individual items and total scores in SSD and non-SSD suicide completers

	SSD n=45 (45/54 = 83.3%)	**non-SSD n=69 (69/254 = 35.0%)**	**p-value**
Individual items			
Agitated behaviour	0.44	0.51	0.65
Self-injury	**0.18**	**1.03**	**<0.01**
Drinking & Drugs	0.71	0.70	0.92
Cognitive Problems	0.31	0.59	0.30
Physical Illness	0.82	0.68	0.99
Halluc./Delus.	**1.22**	**0.29**	**<0.01**
Depressed Mood	**0.89**	**1.80**	**<0.01**
Other mental issues	1.38	1.65	0.64
Relationship	1.07	1.17	0.80
Daily living	0.87	0.87	0.90
Living	0.67	0.59	0.76
Occupational	0.96	0.78	0.70
Total score	9.55	10.52	0.41

SSD: schizophrenia spectrum disorder

3.5.a.4. - Full risk assessment

As described in Table 3.4., only 40 suicide completers (13%) had at least one full risk assessment completed: 19 SSD (35.2%) vs. 21 non-SSD (8.3%) (OR=6.0, 95%CI 2.9-12.3, p<0.01). Mean ± SD total scores were lower in SSD (4.1 ± 2.9) compared to non-SSD (6.2 ± 2.2; t=-2.65, p=0.01). With regard to individual items, patients who had SSD receiving a full risk assessment were less likely to be recorded as having 'suicidal ideation', 'hopelessness', 'lack of control over life', 'impulsivity' or a 'significant loss'; while 'disengagement' was more common in individuals with SSD at borderline statistical significance.

Table 3.4. Risk assessment: Completions rates, individual items and total scores across groups

	Total sample N=40	**SSD n=19 (19/54=35.2%)**	**non-SSD n=21 (21/254 =8.3%)**	**ORs (95% CIs)**	**p-value <0.01**
Individual items					
Suicidal History	26 (65)	11 (57.9)	15 (71.4)	0.55 (0.15-2.05)	0.37
Lethal Method	15 (37.5)	5 (26.3)	10 (47.6)	0.39 (0.10-1.49)	0.16
Plan to end life	8 (20)	2 (10.5)	6 (28.6)	0.29 (0.05-1.68)	0.15
Suicidal ideation	**16 (40)**	**4 (21)**	**12 (57.1)**	**0.2 (0.05-0.81)**	**0.03**
Hopelessness	**18 (45)**	**4 (21)**	**14 (66.6)**	**0.13 (0.03-0.55)**	**<0.01**
Distress	17 (42.5)	7 (36.8)	10 (47.6)	0.64 (0.18-2.27)	0.49
No control of life	**15 (37.5)**	**4 (21)**	**11 (52.4)**	**0.24 (0.06-0.98)**	**0.04**
Alcohol/Drugs	11 (27.5)	7 (36.8)	4 (19.0)	2.47 (0.59-10.40)	0.21
Impulsivity	**18 (45)**	**5 (26.3)**	**13 (61.9)**	**0.22 (0.06-0.84)**	**0.03**
Living alone	18 (45)	8 (42.1)	10 (47.6)	0.80 (0.23-2.80)	0.73
Poor physical health	9 (22.5)	4 (21)	5 (23.8)	0.85 (0.19-3.79)	0.83
Significant loss	**18 (45)**	**5 (26.3)**	**13 (61.9)**	**0.22 (0.06-0.84)**	**0.03**
Disengagement	9 (22.5)	7 (36.8)	2 (9.5)	5.54 (0.98-31.25)	0.06
Recent Discharge	11 (27.5)	5 (26.3)	6 (28.6)	0.89 (0.22-3.59)	0.87
Family History	0	0 (0)	0 (0)	n/a	n/a
Total score		**4.11 ± 2.88**	**6.24 ± 2.19**		**0.01**

SSD: schizophrenia spectrum disorder. OR: Odds Ratio. CI: Confidence Interval

3.5.b. – Case-control study: suicide completers with SSD vs. non-suicidal SSD patients

As alluded to above, of 242,227 SLaM 'active' service users until the 31st December 2013, 635 suicides were identified from the SLaM BRC CRIS. Of these 635 subjects who took their lives, 96 patients (15.11%) had a diagnosis within the schizophrenia spectrum (F2-ICD10). Those who died before 1st January 2007 (n=25) were removed from the analyses since full electronic records before 2007 were unavailable. Thus, 71 suicide completers and 355 controls matched for diagnosis were drawn from the SLaM BRC CRIS.

3.5.b.1. - Sociodemographic and clinical characteristics of the sample

Sociodemographic and clinical characteristics of the whole sample are presented in Table 3.5, including comparisons across groups.

Specifically, while age at first referral did not differ across groups, suicidal patients were significantly younger at the time of first contact with services than controls (34.5 ± 12.6 vs. 39.2 ± 15.2, t=-2.43, p=0.01). Also, when compared with those controls who died from natural causes (n=25), age at death remained significantly younger in the suicidal group (38.5 ± 13.2 vs. 63.2 ± 17.6, t=-6.40, p<0.01).

There was a higher male predominance in cases compared to controls (OR=2.07, 95%CI 1.18-3.65, p=0.01). However, no group differences in marital status, employment or ethnicity were found (see Table 3.5. below for further details).

Table 3.5. Demographic and clinical characteristics: cases and controls

	Total sample 426	**Cases 71 (16.7)**	**Controls 355 (83.3)**	**OR (95% CI)**	**p-value**
Age at first referral (years)	33.9 ± 21.2	30.3 ± 21.1	34.6 ± 21.2		0.12
Age at first contact (years)	**38.4 ± 14.9**	**34.5 ± 12.6**	**39.2 ± 15.2**		**0.01**
Age at death (years)	**44.9 ± 18.0**	**38.5 ± 13.2**	**63.2 ± 17.6***		**<0.01**
Gender (males)	**254 (59.6)**	**52 (73.2)**	**202 (56.9)**	**2.07 (1.18-3.65)**	**0.01**
Marital status (unmarried)	387 (90.8)	66 (92.9)	321 (90.4)	1.36 (0.51-3.60)	0.65
Unemployed	182 (87.1)	28 (82.3)	154 (88.0)	0.64 (0.24-1.72)	0.40
Ethnicity					
White	189 (44.4)	33 (46.5)	156 (43.9)	1.17 (0.66-1.85)	0.70
Black	165 (38.7)	25 (35.2)	140 (39.4)	0.83 (0.49-1.42)	0.59
South-Asian	24 (5.6)	5 (7.0)	19 (5.3)	1.34 (0.48-3.71)	0.57
Others	27 (6.3)	4 (5.6)	23 (6.4)	0.86 (0.29-2.57)	0.79
Social Deprivation (IMD)	31.9 ± 11.3	30.2 ± 12.2	32.3 ± 11.1		0.18

*suicide completers compared with those controls who died from natural causes (n=25). OR: Odds Ratio. CI: Confidence Interval

3.5.b.2. - Service use-related factors

As detailed in Table 3.6., suicide completers were seen by a member of the staff within a shorter period of time from the first referral than controls (medians: 20 vs. 133 days, respectively), although this difference did not reach significance (p=0.12). Suicide completers had received significantly shorter duration of care from the Trust teams (medians-days: 1283 vs. 2517, p<0.01) than controls and a number of cases had been seen by a member of the staff very shortly before the suicide event (median=10 days).

No significant differences in terms of type of last antipsychotic medication prescribed or use of antidepressants emerged from the analyses. Also, the percentage of subjects under CTO did not vary across groups.

Table 3.6. Service use-related factors: cases and controls

	Total sample N=426	**Cases N=71 (71/426=17.7%)**	**Controls 355 (355/426=83.3%)**	**OR (95% CI)**	**p-value**
Length from referral to first contact (median, days)	77	20	133		0.12
Length of service contact (median, days)	**2255**	**1283**	**2517**		**<0.01**
Last face-to-face to death (median, days)	16*	10	63*		0.05
Last hospital discharge to death (median, days)	233*	161	571*		0.24
Antipsychotic					
Oral classic	10 (2.3)	2 (2.8)	8 (2.2)	1.15 (0.24-5.58)	0.70
Oral atypical	200 (46.9)	38 (53.5)	162 (45.6)	1.27 (0.65-2.49)	0.51
Clozapine	24 (5.6)	2 (2.8)	22 (6.2)	0.39 (0.09-1.72)	0.27
Depot	80 (18.8)	12 (16.9)	68 (19.1)	0.75 (0.37-1.52)	0.49
Antidepressant	76 (17.8)	16 (22.5)	60 (16.9)	1.43 (0.77-2.66)	0.31
SCT	18 (4.2)	3 (4.2)	15 (4.2)		1.00

*including those who died from natural causes (n=41) and suicide completers (n=71).
SCT: Supervised Community Treatment. OR: Odds Ratio. CI: Confidence Interval

3.5.b.3. - Cause of death and suicide method

As shown in Table 3.7., there were 25 deaths from natural causes amongst controls, being diseases of the circulatory system (n=6) the most common natural cause of death.

With regard to suicide completers, hanging (n=14) and jumping (n=13) were the most common suicide methods. Twenty-six individuals received an open verdict (undetermined cause of death). There were no suicides by firearms.

Table 3.7. Cause of death - ICD-10 codes

Natural cause	*25*
Neoplasms (C259-710)	3
Endocrine system (E141-149)	2
Mental disorders (F019-209)	3
Nervous System (G060-409)	2
Circulatory System (I119-850)	6
Respiratory System (J180-449)	3
Digestive system (K709-859)	2
Genitourinary system (N390)	3
Unspecified causes of mortality (R99)	1
Unnatural causes	*71*
Hanging (X70)	14
Jumping (X81, X81)	13
Poisoning (X60)	4
Drowning (X71)	4
Cutting (X78)	2
Unspecified means (X84)	8
Undetermined (Y10-34)	26

3.5.b.4 - Health of the Nation Outcome Scale (HoNOS)

61 suicide completers (85.9%) and 315 controls (88.7%) had at least one HoNOS completed. Completion rates did not significantly differ across groups (p=0.54). As detailed in Table 3.8. below, neither HoNOS total score nor did individual items significantly differ between groups.

Table 3.8. Health of the Nation Outcome Scale (HoNOS): Individual items and total scores comparison in suicide completers (cases) and non-suicide completers with SSD (controls)

	Total sample N=376 (376/426=88.2%)	**Cases n=61 (61/71=85.9%)**	**Controls n=315 (315/355=88.7%)**	
Individual items				p-value
Agitated behaviour	0.55	0.39	0.58	0.50
Self-injury	0.15	0.20	0.14	0.25
Drinking & Drugs	0.55	0.57	0.54	0.81
Cognitive Problems	0.58	0.39	0.62	0.09
Physical Illness	0.97	0.79	1.00	0.23
Hallucinations/Delusions	1.16	1.11	1.17	0.96
Depressed Mood	0.82	0.90	0.80	0.93
Other mental problems	1.34	1.41	1.32	0.62
Relationship problems	1.05	1.02	1.06	0.87
Daily living	0.96	0.97	0.96	0.98
Living conditions	0.63	0.82	0.59	0.73
Occupational problems	1.02	1.03	1.02	0.63
Total score	9.74	9.68	9.75	0.89

3.5.b.5. - Full risk assessment

As shown in Table 3.9., 31 suicide completers (43.6%) and 214 controls (60.3%) had at least one full risk assessment completed (OR=0.51, 95%CI 0.30-0.85, p=0.01).

Mean ± SD total scores were lower in suicide completers than controls: 3.19 ± 2.17 vs. 4.52 ± 2.98 (t=3.39, p=0.02), respectively. Differences in individual items are detailed in Table 2.10. Specifically, the following items were significantly associated with an increased risk of suicide completion as follows: 'suicidal history' (OR=4.42, 95%CI 2.01-9.65, p<0.01), 'previous use of violent method' (OR=3.37, 95%CI 1.47-7.74, p=0.01), 'suicidal ideation' (OR=3.57, 95%CI 1.40-9.07, p=0.01) and 'recent hospital discharge ' (OR=2.71, 95%CI 1.17-6.28, p=0.04).

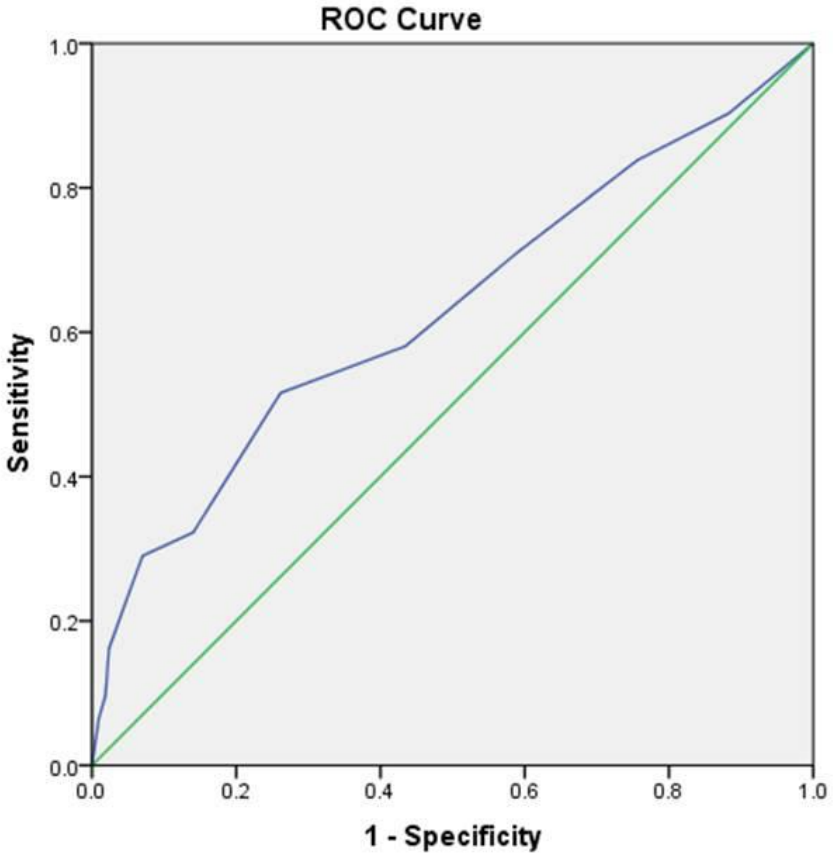
Table 3.9. Full Risk Assessment: Completion rates, individual items and total scores comparison in suicide completers (cases) and non-suicide completers with SSD (controls)

	Total sample N=245	**Cases n=31 (31/71=43.6%)**	**Controls n=214 (214/355=60.3%)**	**ORs (95% CIs) 0.51 (0.30-0.85)**	**p-value <0.01**
Individual items					
Suicidal history	**69 (28.2)**	**18 (58.1)**	**51 (23.8)**	**4.42 (2.01-9.65)**	**<0.01**
Violent method	**41 (16.7)**	**11 (35.5)**	**30 (14.0)**	**3.37 (1.47-7.74)**	**<0.01**
Plan to end life	9 (3.7)	3 (9.7)	6 (2.8)	3.71 (0.88-15.69)	0.09
Suicidal ideation	**27 (11.0)**	**8 (25.8)**	**19 (8.9)**	**3.57 (1.40-9.07)**	**0.01**
Hopelessness	26 (10.6)	6 (19.3)	20 (9.3)	2.33 (0.85-6.35)	0.11
Distress	71 (29.0)	11 (35.5)	60 (28.0)	1.41 (0.64-3.12)	0.40
No control of life	50 (20.4)	10 (32.2)	40 (18.7)	2.07 (0.90-4.74)	0.09
Alcohol/Drugs	78 (31.8)	14 (45.1)	64 (29.9)	1.93 (0.90-4.15)	0.10
Impulsivity	81 (33.1)	11 (35.5)	70 (32.7)	1.13 (0.51-2.49)	0.84
Living alone	95 (38.8)	10 (32.2)	85 (39.7)	0.72 (0.32-1.61)	0.55
Poor physical health	71 (29.0)	5 (16.1)	66 (30.8)	0.43 (0.16-1.17)	0.14
Significant loss	63 (25.7)	9 (29.0)	54 (25.2)	1.21 (0.53-2.79)	0.66
Disengagement	91 (37.1)	14 (45.2)	77 (36.0)	1.46 (0.68-3.13)	0.33
Recent discharge	**42 (17.1)**	**10 (32.2)**	**32 (15.0)**	**2.71 (1.17-6.28)**	**0.04**
Family history	9 (3.7)	0 (0)	9 (4.2)	n/a	0.62
Total score	**3.3 ± 2.3**	**4.5 ± 2.9**	**3.1 ± 2.2**		**0.02**

SSD: schizophrenia spectrum disorder. OR: Odds Ratio. CI: Confidence Interval

ROC curve analyses for risk assessment total scores (see figure 3.3 below) found the most optimal cut-off point to be 3-4, with a sensitivity of 0.58 and specificity of 0.57. The area under the curve was 0.63 (95%CI 0.51-0.74), which is shown in figure 1 below. If we assume that the prevalence of suicide in these patients is 5% (Palmer et al., 2005), the positive predictive value was 0.06, while the negative predictive value was 0.96.

Figure 3.3. ROC Curve for risk assessment total score



3.5.b.6. - Multivariable binary logistic regression models

Age at first contact with services, gender and four items from the risk assessment, namely suicidal history, use of violent method, suicidal ideation and recent discharge from hospital, which had been significantly associated with suicide completion in the above univariate analyses, were added to the model (see Table 3.10).

However, only age at first presentation (OR=0.94, 95%CI 0.90-0.98, p<0.01), suicidal history (OR=4.07, 95%CI 1.80-9.18, p<0.01) and suicidal ideation (OR=3.06, 95%CI 1.14-8.20, p=0.03) survived as significant predictors of suicide completion. The final binary logistic regression model shown in table 3.11 (χ^2=29.771, df=3, p<0.01) explained 21.5% (Nagelkerke R^2) of the variance on suicide completion and overall correctly classified 86.5% of the subjects. Specifically, 98.6% of non-suicides and 3.2% of suicides were predicted by the model.

Table 3.10. Multivariable regression model: suicide completion as the dependent variable

	B	SE	Wald	p	OR	95% CI
Age at first contact	**-0.06**	**0.02**	**8.84**	**<0.01**	**0.94**	**0.90 - 0.98**
Gender	0.32	0.46	0.47	0.49	1.37	0.55 - 3.41
Suicidal history	**1.20**	**0.56**	**4.60**	**0.03**	**3.31**	**1.11 - 9.89**
Violent method	0.32	0.61	0.28	0.59	1.38	0.42 - 4.55
Suicidal ideation	**1.11**	**0.52**	**4.54**	**0.03**	**3.03**	**1.09 - 8.39**
Recent hospital discharge	0.80	0.48	2.79	0.09	2.23	0.87 - 5.72

Model χ^2=33.599, df=6, p<0.001.

Table 3.11. Final regression model: suicide completion as the dependent variable

	B	SE	Wald	p	OR	95% CI
Age at first contact	**-0.06**	**0.02**	**9.31**	**<0.01**	**0.94**	**0.90 - 0.98**
Suicidal history	**1.40**	**0.41**	**11.42**	**<0.01**	**4.07**	**1.80 - 9.18**
Suicidal ideation	**1.12**	**0.50**	**4.94**	**0.03**	**3.06**	**1.14 - 8.20**

Model χ^2=29.771, df=3, p<0.001

3.6. – Discussion

3.6.a. – Principal findings

In a large clinical case register sourced from electronic mental health records linked to a national death certification database, I investigated characteristics of patients with SSD dying from suicide. First, I compared these subjects with those patients without SSD who took their lives. Second, I conducted a case-control study in order to examine potential predictors of suicide in SSD, including engagement, which is related to insight, by comparing subjects with SSD who completed suicide with those individuals with SSD who did not complete suicide in the same time frame.

Thus, a population of secondary mental healthcare users who completed suicide over the study period (2007-2013) was identified from our case register. Nearly one in five of the suicide completers had been diagnosed with schizophrenia spectrum disorders (SSD), which is approximately double that in previous reports (Arsenault-Lapierre et al., 2004), although this may reflect the high prevalence of psychotic disorders in South-East London (Fearon et al., 2006).

When suicide completers with/without SSD were compared, I found that SSD patients were more likely to have full risk assessment and HoNOS documented than non-SSD subjects. However, the classic risk factors evaluated by these instruments were significantly more common in non-SSD patients (Lopez-Morinigo et al., 2014b). This led me to designing the second study in which I compared SSD patients who took their lives (cases) with controls, i.e. SSD patients who did not end their lives (Lopez-Morinigo et al., 2016).

Thus, early first contact with mental health services, suicidal history and suicidal ideation were associated with suicide completion. Owing to low frequency and lack of statistical power, suicide completion in SSD is not a predictable occurrence, with only 21.5% of the variance explained by the final regression model, yet older age at first contact with mental health services and lack of both suicidal history and suicidal ideation are useful protective markers indicative of those less likely to end their own lives. As postulated, disengagement increased risk of suicide, although this relationship did not reach statistical significance (Lopez-Morinigo et al., 2016).

3.6.b. – Sociodemographic and clinical variables

Several differences were found in sociodemographic characteristics between SSD and other diagnoses. Specifically, those subjects with SSD died at a younger age, they tended to be more commonly of Black origin and they were more socially deprived than non-SSD suicide completers, which replicated previous findings in our catchment area with non-suicide samples (Kirkbride et al., 2008; Aschan et al., 2013). Thus, while some previous studies have shown an association between psychosis and Black ethnicity (Fearon et al., 2006), other groups have raised concerns regarding a diagnostic bias towards psychosis in Black people (Gara et al., 2012; McKenzie, 2012). However, previous studies from our group, which carefully considered the above potential bias in the methodology, revealed a link between Black Ethnicity, social deprivation and psychosis in our catchment area (Morgan et al., 2010a). Hence, the findings concerning differences between patients with and without SSD who died by suicide in terms of social deprivation and ethnicity might reflect specific sociodemographic characteristics of our population irrespective of such a fatal outcome despite previous literature showing a relationship between ethnicity and suicide (McKenzie, 2012; Al-Sharifi et al., 2015).

In keeping with the above, the case-control study revealed that those subjects with SSD who died by suicide had their first contact with mental health services at a younger age than SSD controls, which is consistent with previous studies showing an increased suicide risk in early psychosis (e.g. Dutta, 2010), although late onset behaved as a risk factor in an epidemiological study from Taiwan (Kuo et al., 2005). Moreover, when suicide completers were compared with those controls who died from natural causes (see Table 3.5.), these controls were found to have a significantly longer life expectancy, 63 vs. 38 years, thus providing further support for suicide prevention in early psychosis. Regarding gender, I replicated an increased risk of suicide completion in males (Hu et al., 1991; De Hert et al., 2001; Sinclair et al., 2004; Kuo et al., 2005; Hawton, 2005).

Of relevance, neither being unemployed nor unmarried was associated with increased suicide risk, which was, however, consistent with a previous meta-analysis (Hawton et al., 2005). Also, despite previous literature showing a relationship between ethnicity and suicide (Hawton et al., 2005; McKenzie et al., 2012; Al-Sharifi et al., 2015), I failed to replicate such an association. However, it should be noted that being single, unemployed and of Black ethnicity

are characteristics of a majority of people with psychosis living in south-east London (Fearon et al., 2006; Kirkbride et al., 2008).

3.6.c. – Suicide method

With regard to suicide method, I found that while hanging was the most common suicide method in the whole sample, patients with SSD were more likely to have used 'jumping' (from an height or in front of a vehicle) to take their lives, consistent with previous literature on suicide completion and methodology (Hawton & van Heeringen, 2009; Nielssen et al., 2010; McGirr et al., 2006; McGirr & Turecki, 2008).

Hence, in line with previous literature (Hu et al., 1991; De Hert et al., 2001; McGirr et al., 2006; McGirr & Turecki, 2008; Hawton et al., 2009; Nielssen et al., 2010; Dutta et al., 2010), I replicated that hanging and jumping (from an height or in front of a vehicle) were the most common suicide methods in patients with SSD, although patients with SSD were reported to kill themselves by taking overdoses in Finland (Heilä, 1997). Of note, no suicides by firearms were identified in the study, which is in line with previous reports from the UK (e.g. Dutta et al., 2010) and other European countries (e.g. De Hert et al., 2001), thus reflecting the restrictions to firearms access compared with the USA. It should be noted that firearms are ubiquitous in the USA and the high level of firearm ownership has been directly associated with an increased risk of firearm-related mortality (Bangalore & Messerli, 2013), including suicide (Kposowa et al., 2016).

In keeping with this, limiting availability of lethal methods has been demonstrated to reduce suicide rates at a population level (Kreitman, 1976; Hawton & van Heeringen, 2009). Also, restricting access to suicide hotspots such as heights through safety barriers (e.g. (Bennewith et al., 2007) and railway lines by installing platform edge doors (Law et al., 2009) has been reported to reduce overall suicide rates at such places (Cox et al., 2013). Hence, installing physical barriers in bridges, tall buildings and railway stations, particularly when placed near psychiatric hospitals, given our replication finding concerning the increased suicide risk after discharge, may prevent patients with SSD from suicide (Lopez-Morinigo, 2014b). Although restricting access to means of hanging appears to be more challenging, such a planned method requires a longer period of time during which these individuals may be identified through welfare checks or Home Treatment Team visits.

3.6.d. – Health of the Nation Outcome Scale (HoNOS) and risk assessment ratings

Of relevance, it seems that clinicians deem patients who have SSD at greater risk of suicide than other patients and they are therefore more likely to have received a full risk assessment, as well as having a higher likelihood of HoNOS completion, which is relatively in contrast to previous literature (Pedersen et al., 2014). However, the above instruments may have been completed due to concerns raised regarding other risks such as violence and/or self-neglect. Interestingly, known suicide risk factors, which are evaluated by these tools, tended to be less commonly recorded as present in those who have SSD than in subjects with non-SSD. Also, the predictive models were of little value to identify those individuals with SSD who completed suicide (as explained below).

3.6.d.1. – Health of the Nation Outcome Scale (HoNOS)

With regard to HoNOS items in our sample of suicide completers, while symptoms severity such as depressed mood and 'hallucinations & delusions' differed across diagnostic groups, as expected, interestingly 'social needs', 'cognitive deficits' or 'alcohol/drugs problems' did not (significantly) vary between suicide completers with SSD and without SSD. In this regard, it could be speculated that the care package provided to these patients by the Trust succeeded in meeting their complex social needs and accordingly the most recent HoNOS scores regarding social needs did not reveal differences across the above diagnostic categories. An alternative explanation might be that there are no associations between (met/unmet) social needs, psychiatric diagnosis and suicidality. In keeping with this, the case-control study failed to find these relationships.

3.6.d.2. – Risk assessment

Interestingly, known suicide risk factors tended to be less commonly recorded as present in those who have SSD than in subjects with non-SSD. Of relevance, disengagement was found to be (significantly) more frequent in SSD than non-SSD suicide completers, however. Despite the above, half of suicide completers with a SSD had been seen by a member of the staff shortly before such a fatal outcome, which is in line with previous studies showing the relative inability of clinicians to predict imminent suicide risk in individuals with SSD under their care (Heilä et al., 1997; Tarrier et al., 2006).

Of note, SSD controls were more likely to have a full risk assessment documented than suicide completers, which was relatively in contrast to previous literature (Pedersen et al., 2014). Alternatively, this difference may have been due to the longer care received by non-suicidal subjects. Also, a full risk assessment may have been completed due to concerns raised regarding other clusters of risk such as violence and/or self-neglect (Wu et al., 2012), as alluded to above. Moreover, recording of risk assessment has been reported to be, to some extent, circular. Specifically, some data from risk assessments following self-harm are more likely to be recorded if episodes result in a specialist assessment (Kapur et al., 2008).

In line with our hypotheses and previous research (Hu et al., 1991; De Hert et al., 2001; Sinclair et al., 2004; Hawton et al., 2005; Dutta et al., 2010) I replicated the role of suicidal history and suicidal ideation (Hawton et al., 2005; Popovic et al., 2014), previous use of a violent method and recent hospital discharge (NCISH, 2015) in suicide risk in psychosis. These factors were, however, more common in patients with non-SSD who died by suicide. Moreover, no associations of hopelessness, impulsivity, alcohol/drugs misuse, living alone or significant losses with suicide completion were found in line with previous literature in suicide and psychosis (McGirr et al., 2006; Dutta et al., 2011). Also, most of suicide completers with SSD did not have most of the factors evaluated by the risk assessment with the exception of 'suicidal history'. Hence, suicide in SSD may represent a challenge to the classic suicide model (Mann et al., 1999), particularly regarding the role of hopelessness (Beck et al., 1990) and impulsivity (Mann et al., 1999; Baca-Garcia et al., 2005a).

In addition, the ROC curves showed that risk assessment total scores performed poorly in terms of sensitivity, specificity and positive predictive value, while the test had a very high negative predictive value, which is in full agreement with a recent systematic review of risk assessment scales for predicting repeat self-harms in suicide attempters (Quinlivan et al., 2016).

Of relevance, a history of disengagement was found to be present in nearly half of the suicide completers with SSD, which was a non-significantly higher proportion than in non-SSD patients. However, most of suicides in the SSD group occurred shortly after having been seen by a member of the staff, which is in line with previous studies showing the relative inability of clinicians to predict imminent suicide risk in individuals with SSD under their care (Hu et al., 1991; Heilä et al., 1997; Tarrier et al., 2006; NCISH, 2015).

3.6.e. – Service use-related factors

In terms of mental health services use-related factors, those who completed suicide, were also more likely to have a suicide history, as discussed below, tended to have a shorter interval between the referral and first contact with services. These findings are in full agreement with two previous first-episode psychosis studies which suggest that suicidal behaviour preceding first contact with services appears to shorten the duration of untreated psychosis (DUP), which in both studies was reported to be a high-risk period, leading the patient to receive psychiatric attention earlier (Upthegrove et al., 2010; Lopez-Morinigo et al., 2014a). Moreover, psychotic symptoms in adolescents appear to be a clinical marker for future suicidal behaviour both in the general population (Kelleher et al., 2012; Kelleher et al., 2013) and in clinical samples (Kelleher et al., 2014).

Also, the duration of care was significantly shorter in those who died from suicide compared to non-suicidal patients but this is most likely the consequence of suicide bringing care to a halt. More importantly, I replicated the high suicide risk during the immediate period after hospitalization (Hu et al., 1991; Sinclair et al., 2004; Heilä et al., 1997; De Hert et al., 2001; NCISH et al., 2015). In particular, half of our suicide completers took their lives over the 6-month period after being discharged from a psychiatric ward. Hence, close monitoring over that period of time should be strongly recommended (Popovic et al., 2014; NCISH, 2015).

There have been recommendations on the use of antidepressants (Siris, 2000; Siris et al., 2001; Sinclair et al., 2004) and depot antipsychotics (Sinclair et al., 2004) for suicide prevention in schizophrenia and related disorders. However, our findings do not provide further support for these guidelines. Similarly, in spite of the anti-suicidal properties of clozapine (eg. Meltzer et al., 2003; Bourgeois et al., 2004), I was unable to show a particular benefit for this drug. These results were in line with previous case-control studies (De Hert et al., 2001; Kuo et al., 2005), which all may have lacked sufficient statistical power to test the role of the above interventions in suicide prevention in psychosis.

Also, receiving community mental healthcare under restriction in accordance with the UK Mental Health Act 1983 (Amended 2007) (DoH, 2008), which is known as Community Treatment Order (CTO), did not appear to prevent patients with SSD from suicide. These findings seem to be consistent with the UK National Confidential Inquiry into Suicide and Homicide 2015 report (NCISH, 2015). In particular, there were 42 suicides in patients subject to a community treatment order (CTO) between 2009 and 2013 in England. Moreover, the suicide

rate was significantly higher in CTO patients (2.0 per 1,000 CTOs in 2009-2012) than in the general population (9.4/100,000-year), as expected, since CTO patients are selected for risk on hospital discharge. Indeed, 19 of the 42 deaths (45%) occurred within 3 months of hospital discharge, which is a high-risk period (Hawton et al., 2005), as replicated by our findings. In addition, 6 patients who died from suicide while subject to a CTO had been non-adherent with drug treatment in the month before death and 9 had missed the last appointment with services; 2 had both refused treatment and missed the last appointment. Therefore, 31% of those who died from suicide were not receiving care as intended despite CTO powers, which suggests that gaining insight, rather than legal restrictions, may improve engagement with services, thus reducing suicide risk.

Although a recent randomized controlled trial (RCT) showed that CTO did not reduce the number of readmissions over a 12-month follow-up in patients with psychotic disorders (Rugkåsa et al., 2015), no data on suicidal behaviour were reported. Hence, further research in this controversial area is warranted in order to clarify whether CTOs can help to tackle suicide in SSD. However, a randomized controlled trial aimed to answer such a research question raises ethical issues since in the above study (Rugkåsa et al., 2015) patients in the control group were not receiving care voluntarily but under Section 17 of the UK Mental Health Act (DoH, 2008). In other words, the RCT to clarify this matter would have to compare patients under CTO with high-risk subjects (hence, probably fulfilling criteria for CTO according to the treating consultant) discharged from hospital without restrictions.

3.6.f. – Strengths and limitations

This study focused on the rare outcome of suicide completion. Moreover, by using a large case register linked to national mortality data all those patients with a diagnosis of SSD who were receiving secondary mental healthcare in our catchment area and died by suicide over 2007-2013 were included in the study with the only exception of those who completed suicide outside the UK. Of note, most of patients were followed-up over a prolonged period (median=6.17years). Since only a small proportion of patients living in South-East London receive private mental health care, the sample is likely to be representative. In addition, a wide range of demographic and clinical variables, including service use-related factors and specific scales such as HoNOS and 'risk assessment', were analysed.

However, these results should be considered in the light of several limitations. First, the sample was formed of secondary mental health services users living in south-east London, an inner-urban area, and results may not generalise to people receiving mental health input from primary care or those in rural areas. Second, HoNOS and risk assessment ratings were not available for a number of participants. Also, I can speculate that those patients who had HoNOS and risk assessment completed were deemed 'at-high-risk' by their clinical teams. In addition, although just the last HoNOS and risk assessment were considered for the analyses, risk factors evaluated by those instruments may have changed from that point to death. Hence, the findings regarding HoNOS and risk assessment ratings should be interpreted with caution. Also, it should be noted that a wide range of variables have been taken over a prolonged period of time, which also varies across the study patients, who ranged from having one single assessment to several years under secondary mental healthcare, thus reflecting the real-world nature of our data. Finally, other non-tested variables such as premorbid personality (Giner et al., 2013) and premorbid adjustment (Ayesa-Arriola et al., 2015) may contribute to risk of suicide.

3.6.g. – Implications and directions for future research

Risk of suicide completion in patients with SSD appears to be highly unpredictable. In particular, early first contact with mental health services, previous suicidal history and suicidal ideation were found to be the strongest predictors of suicide completion in patients with SSD, which is in line with recent recommendations to tackle suicide in schizophrenia (Popovic et al., 2014). However, given the low predictive value of our model to identify suicide completers, which was also consistent with the short time from last contact with a mental health professional to dying from suicide, no suicide prevention strategies at an individual level can be drawn from our findings.

Also, nearly half of the suicide completers had a history of disengagement with services, although the differences did not reach significance. Hence, there are grounds to consider that insight, which has been associated with adherence (Amador & David, 2004), might be a protective factor for suicide in schizophrenia spectrum disorders via increased compliance and engagement, which has been demonstrated to reduce suicide rate both in early psychosis (Barrett et al., 2015) and mixed samples (Sinclair et al., 2004; Hawton et al., 2005) despite common assertions to the contrary (see (Lopez-Morinigo et al., 2012)).

In addition, stigma, which prevents patients from receiving proper care (Alonso et al., 2007), may play a relevant role in suicide risk in patients with SSD who disengage from secondary mental health services (Thornicroft & Mansella, 2013). Nevertheless, more research is needed to test whether anti-stigma campaigns can reduce suicide rates both at a population level and in high-risk groups such as mental health service users with SSD.

3.7 – Chapter Summary

In line with our hypotheses, early first contact with mental health services, suicidal history and suicidal ideation were associated with suicide completion. Owing to low frequency and lack of statistical power, suicide completion in SSD is not a predictable occurrence, with only 21.5% of the variance explained by the final regression model, yet older age at first contact with mental health services and lack of both suicidal history and suicidal ideation are useful protective markers indicative of those less likely to end their own lives.

Interestingly, disengagement from services was found to be a risk factor for suicide completion in patients with SSD. Hence, there are grounds to consider that insight may reduce suicide risk in patients with SSD via improved adherence, which is in line with the PhD hypotheses detailed in chapter 2 (section 2.5), particularly H5.

Chapter 4 - Suicidal behaviour in early psychosis. Findings from the Genetics and Psychosis (GAP) study (London, UK)

4.1. – Introduction

This chapter describes the predictors of suicidal behaviour in a 3-year follow-up first-episode psychosis (FEP) cohort from London (UK). In particular, the role of three insight dimensions - recognition of having a mental illness, symptom relabelling and awareness of the need for treatment - in suicidal acts (including suicide attempts and suicide completion) over the follow-up period was investigated. Also, these analyses were adjusted for a set of demographic and clinical variables, which may mediate/confound the above relationships and therefore influence the rate of suicidal acts.

Some of the analyses presented below have been published as a peer-reviewed article, namely the influence of suicidal history on insight levels at first presentation with psychosis (Lopez-Morinigo et al., 2014a). However, for the purposes of this thesis I have focused on suicidal events 'after' first presentation with psychosis, thus considering survival to a first suicide attempt (including suicide completions) over the follow-up period in relation to insight levels at baseline.

4.2. - Background

The rate of suicide in schizophrenia has been recently reported to be approximately 5% (Palmer et al., 2005). More recently, a large epidemiological study with a cohort of FEP patients (n=2,783) who were followed-up over 10 years has estimated this risk at 1.9% (Dutta et al., 2010). While these figures are lower than the previously quoted estimate of 10% (Miles, 1977; Caldwell & Gottesman, 1990), suicide risk in schizophrenia and related disorders remains unacceptably high, representing the largest single cause of excess mortality in schizophrenia (Brown, 1997; Saha et al., 2007; Dutta et al., 2012). Moreover, between 15-26% of FEP patients have made at least one suicide attempt by their first treatment contact and 2–11% attempt to end their lives over the first year after treatment onset (Melle et al., 2006). Yet, it remains unknown the number of patients with an undiagnosed first episode of psychosis who take their lives within the context of the onset of a psychotic illness.

A seminal meta-analysis by Hawton and colleagues published in 2005 summarised suicide risk factor studies in schizophrenia. Of note, previous depressive disorder, previous suicide attempts, drug misuse, agitation or motor restlessness, fear of mental disintegration and recent loss were reported to be the most robust risk factors. Interestingly, compliance with treatment was demonstrated to reduce suicide risk (Hawton et al., 2005; Qin et al., 2006). In keeping with the above, a more recent systematic review in first-episode psychosis (Pompili et al., 2011) revealed that suicide risk factors in psychosis are stage-related.

Regarding risk changes over time, some studies showed that the periods of the highest risk of suicide in FEP patients are shortly before and after hospitalization (Melle et al., 2006; Harvey et al., 2008: Ayesa-Arriola et al., 2015). One study (Flanagan & Compton, 2012) found that nearly one-quarter of patients endorsed a history of suicidal ideation in the two weeks prior to first admission and they should also be carefully monitored at initiating treatment and over the early stages of the course of the psychotic illness. However, it should be pointed out that such a history may influence clinicians in the decision to admit and hence this observation is somewhat circular.

Studies testing the role of insight in risk of suicide in psychosis have attracted interest although so far results are inconclusive (Hawton et al., 2005; Pompili et al., 2011; Lopez-Morinigo et al., 2012; Melle & Barrett, 2012;). Insight has been suggested to increase suicide risk, particularly in early psychosis, due to the so-called 'demoralization syndrome' (Drake & Cotton, 1986), a notion widely held amongst clinicians. Briefly, those patients who are more aware of having such a devastating illness, i.e. those with greater insight, would tend to become depressed and develop feelings of hopelessness, including a potential increased risk of suicide. On the other hand, denial of illness and subsequent poor compliance with treatment was found to increase suicide risk in schizophrenia (Hawton et al., 2005). Hence, there are grounds to consider that insight, which is linked with compliance (Amador & David, 2004), may reduce suicide risk via improved adherence.

Also, it could be argued that suicidal behaviours preceding first presentation with psychosis, which is the strongest predictor of further suicidal events (Hawton et al., 2005; Pompili et al., 2011), may affect insight levels at that point. As detailed in chapter 2, a few cross-sectional studies conclude that insight is a risk factor for suicide on the basis that those patients with greater insight had a higher prevalence of previous suicidal acts than those with poorer insight (Harvey et al., 2008; Gonzalez, 2008; Schennach-Wolff et al., 2009). This is taken

to support notions that acquiring insight may damage self-esteem and lead to depression (Drake & Cotton, 1986; Restifo et al., 2009). However, such results may be subject to both selection and recall bias (Lopez-Morinigo et al., 2012). Furthermore, applying the temporality criterion of causality (Hill, 1965) may lead me to suggest that, on the contrary, suicidal behaviours preceding FEP may influence later insight at first presentation, either directly or through some mediating variables. To my knowledge, only my 2014 study (Lopez-Morinigo et al., 2014a), which is presented in this chapter, has investigated the potential influence of suicidal acts preceding FEP on insight dimensions at first presentation (at baseline).

Thus, in this chapter I will present research (now published: Lopez-Morinigo et al., 2014a) concerning the association of previous suicidal history with multiple insight dimensions at first contact with services using data from the Genetics and Psychosis (GAP) study, which recruited a sample of incidence cases with a FEP. In particular, I hypothesised that FEP patients with a past history of suicidal behaviour would have a greater 'awareness of mental illness' and 'symptom relabelling' at first presentation than non-suicidal FEP patients. This is because prior suicidal events might have been a consequence of certain psychotic symptoms such as distress or hallucinations and therefore a suicidal history might help these patients to more easily recall at the time of insight assessment such psychotic phenomena and the (potential) illness underlying them. On the other hand, 'compliance' should be less associated with such antecedents since suicidal patients have a tendency to be less open to receiving external help, i.e. they tend to try and deal with problems themselves.

Next I will present the results of having followed-up this FEP cohort over a median period of 3 years in order to ascertain the influence of each insight domain on later risk of suicidal behaviours, including suicide attempts (SA) and suicide completions (SC), i.e. to test the hypotheses formulated in chapter 2 (section 2.5).

4.3. - Aims and Objectives

4.3.a. – Descriptive aims and objectives

- To describe the distribution of insight dimensions according to the outcome of suicidal behaviours, including both suicide attempts and suicide completions.

4.3.b. – Analytical aims and objectives

- To investigate whether there is an association between a history of suicidal behaviours before first presentation with psychosis and insight levels at that time of first assessment.
- To adjust the above analyses for a set of potential confounders in order to determine independent predictors of insight at baseline, including the role of previous suicidal history.
- To calculate the case fatality of this FEP sample over the 3-year follow-up period.
- To identify the risk factors associated with suicidal behaviours in a FEP cohort over a 3-year follow-up period.
    - And to determine whether there is an association of insight levels with risk of suicidal behaviours over the 3-year follow-up.
- To test for potential interactions between insight dimensions and other clinical and demographic variables related to risk of suicidal behaviour.
- To formulate a model, based on a multivariable Cox regression analysis of the above baseline variables, including insight dimensions, for predicting suicidal behaviours over the 3-year follow-up period.

4.4. - Method

4.4.a. – Participants, study design, setting and follow-up

The data for this part of the thesis are derived from the National Institute of Health Research Biomedical Research Centre (NIHR BRC) Genetics and Psychosis (GAP) study. All patients aged 18-65 years who presented with a FEP to the South London and Maudsley NHS Foundation Trust, which provides secondary mental healthcare to four boroughs in South-East London (Southwark, Lambeth, Lewisham and Croydon), were approached within the first week of admission. In total, N=252 incidence FEP patients met GAP inclusion criteria and agreed to take part in the study (i.e. approximately 44% of those who were approached). Those who had been administered the expanded version of the Schedule for the Assessment of Insight (Kemp and David, 1997; Sanz et al., 1998) at the study inception (n=112) were included in this study.

The GAP study obtained ethical approval from the local research ethics committees and participants provided written informed consent.

Inclusion criteria were fulfilling ICD-10 (WHO, 1993) criteria for psychosis (codes F20-F29 and F30-32 with psychotic features) according to the clinical team, including assessment by at least one senior psychiatrist. Exclusion criteria were moderate to severe learning disabilities as defined by ICD-10 (WHO, 1993), poor English fluency (i.e. the participant would require an interpreter), a history of previous contact with health services (GP or Psychiatric) for psychosis and a known organic cause of psychosis. In addition, given the specific aims of this thesis, only those patients with an insight assessment at baseline through the Schedule for Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997) could be included.

The GAP study, which first started in 2004, has a cross sectional case-control design and investigates a wide variety of potential risk factors, biological markers, physical health measures, psychological, psychopathological, neurocognitive and socio-demographic differences between patients presenting to psychiatric services for the first time with psychosis and healthy controls. A summary of the study battery can be seen in box 4.1.

Box 4.1. – GAP study battery summary

Fasting blood sample (esp. investigating DNA, proteomics, glucose levels, transcriptomics) and physical health measures.

Questionnaires (focusing on childhood experiences, stress, physical health, drug use).

Measures of psychopathology (including the PANSS and others).

Salivary cortisol sampling.

Brain scan (structural and functional MRI, Diffusion Tensor Imaging).

Neuropsychological battery.

Screening was carried out through a variety of channels to ensure the maximum level of recruitment and minimise selection bias. Researchers took a weekly list of all new admissions to SLaM wards which may assess or treat psychotic patients, and screened patients' clinical notes to assess for suitability. This was supplemented with regular communication with doctors, nurses and healthcare assistants on the wards. The study aimed to approach patients presenting with a functional psychosis within the catchment area. This was done as soon as possible after admission (and no more than 6 months after their first contact with services). This involved regular updates from ward teams regarding new patients, and appropriate patients usually being approached first by a member of staff, before the research team contacted them. Recruitment from wards was supplemented with recruitment from community teams and home treatment teams (<10% of patients) where resources were available to cover these.

Once a patient was deemed to be suitable and after checking with the ward team that it would not be detrimental to the patient or of undue risk to the researcher, participants would be approached, invited to participate in the study and given information and consent sheets. If patients were willing and able to give informed consent, they would read through the consent form, confirm that they fully understood the study, were assured that they could drop out at any time without giving any reason and sign the forms. Some patients would be approached on several occasions to ensure they had fully understood the information. If patients asked not to be approached again, this was, of course, honoured.

Once a patient consented, assessments were carried out as quickly as possible in the minimum necessary number of visits, taking into account the attention span and availability of the patient. Assessments were either carried out on the ward, at the team base or at the patient's home.

All recruitment and assessments were carried out by trained psychologists or psychiatrists and under the overall supervision of senior researchers and principal investigators. One of those assessments consisted of an interview using the Schedule for the Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997), which is detailed below. The patients who took part in the SAI-E interview formed the subsample for this thesis.

In order to obtain suicide-related information on each patient at 3 years (minimum follow-up period based on power calculations reported in section 4.4.c.1. below), all cases were traced through a procedure performed by several GAP researchers which included contacting the patient via a phone call and/or a letter and contacting the GP. Also, data from this cohort were linked with the Office for National Statistics (ONS), which in the UK records the official cause of death by using ICD-10 codes.

4.4.b. – Measures

4.4.b.1. – Premorbid, sociodemographic and clinical variables

Information was obtained from patients, relatives and medical records in the GAP study. This included sex, age at admission, age at onset and duration of untreated psychosis (DUP), which was estimated from the patient's medical notes with the Nottingham Onset Schedule (Singh et al., 2005). The time from the date of the first continuous psychotic symptom (lasting at least a week) to the date of commencing on antipsychotic medication (having taken 75% of doses within the following month) was taken.

Other sociodemographic variables collected were: level of education, relationship status ("married" vs. "unmarried"), living status ("alone" vs. "other"), employment status ("employed", "student" or "unemployed"), cannabis use (yes/no) and alcohol use (yes/no). In particular, all participants were asked about their use of illicit drugs and those who reported ever using cannabis were interviewed using the Cannabis Experience Questionnaire (see Di Forti et al., 2009) to confirm cannabis use and further related variables which were not used in this study.

4.4.b.2. – Insight

The Schedule for Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997) was used to evaluate insight. This is a semi-structured interview easily applicable to clinical practice (Sanz et al., 1998) that provides several separate insight scores based on David's model (David, 1990): 'awareness of mental illness', 'relabelling of psychotic symptoms as abnormal' and 'compliance'. Researchers were trained by the scale author demonstrating good inter-rater reliability (Morgan et al., 2010b). Of note, the SAI-E was found to strongly correlate with other insight scales, including the Scale to Assess Unawareness of Mental Disorder (SUMD) (Sanz et al., 1998), which was used in chapter 7 (Santander cohort). This allowed cross-comparison of the findings from these two cohorts, which are presented in the general discussion (Chapter 8).

4.4.b.3. – Neurocognitive tests

The National Adult Reading Test (NART) (Nelson & Willison, 1991) was used to evaluate the premorbid Intelligence Quotient (IQ). Also, the short version of the Wechsler Adult Intelligence Scale Revised (WAIS-R, Wechsler, 1981) provided an accurate estimate of the current IQ (full scale).

Executive function was assessed by the Trail Making Test (Reitan, 1958), which involves connecting numbers (Trails A) or alternating numbers and letters (Trails B). The time (in seconds) taken to complete the task was the dependent variable. Subtracting time to complete Trails A from Trails B gives an overall measure of executive function, after having controlled for the effect of processing speed.

4.4.b.4. – Psychopathological symptoms

With regard to psychopathology, in the GAP study five psychopathological dimensions were measured with the Positive and Negative Symptoms Scale for Schizophrenia (PANSS, Kay et al., 1987) based on a previous systematic review of PANSS factor analyses (Wallwork et al., 2012): positive (items P1, P3, P5 and G9), negative (items N1, N2, N3, N4, N6 and G7), disorganization (items P2, N5 and G11), mania (items P4, P7, G8 and G14) and depression (items G2, G3 and G6).

4.4.b.5. – Suicide attempts information

Suicidal behaviours were taken from medical records and defined as 'any potentially self-injurious behaviour for which the person intended to kill himself/herself' (O'Carroll et al., 1996). In particular, any suicidal act before first contact with psychiatric services and any further suicidal behaviours were registered, which included suicide attempts and suicide completions. Information on suicidal behaviour was available for the entire sample.

In addition, I identified all occurrences of death and emigration in the cohort over the follow-up period via a person-tracing procedure conducted by the Office for National Statistics (ONS) for England and Wales and the General Register Office (GRO) for Scotland using name, sex, date of birth, and last known address. For all identified deaths, principal underlying causes of death were determined according to the International Classification of Diseases, 10th revision (ICD-10), as recorded on copies of death certificates obtained from ONS. I classified as 'suicides' those subjects with the following ICD-10 codes of death according to the ONS: X60–X84 and Y10–Y34. Of note, in the UK most 'open verdicts' (ICD-10 codes Y10–Y34) are likely to be suicides since the coroner, who under UK law certifies the cause of death, needs to provide evidence (of suicide) 'beyond reasonable doubt' (Linsley et al., 2001).

4.4.c – Statistical analysis

The Statistical Package for Social Science version 22.0 (SPSS Inc., Chicago, IL, USA) was used for performing the statistical analyses. Descriptive analyses and comparison of patient characteristics, including the aforementioned demographic and clinical variables, were undertaken using chi-square, t-tests and Mann-Whitney U tests as appropriate.

First, predictors of insight dimensions at baseline were investigated through binary logistic regression models in order to precisely test the influence of suicidal history on insight levels after adjusting the analyses for potential mediating variables.

Second, all patients were entered into a survival analysis with the end date being the date of first suicide attempt (or suicide completion where appropriate) or the censoring point, i.e. either the date on which the patient was last known to be alive or the end of the follow-up study period, which commenced at the time of discharge from hospital or after first contact to services in those patients who were not admitted at first presentation.

Risk of suicide over the follow-up period was calculated by considering the proportion of patients who died from suicide of the total initial sample size (i.e. those who were lost to follow-up were included in the denominator), which is known as case-fatality (Palmer et al., 2005).

Survival analyses (Kaplan-Meier Curves and log-rank tests) were performed to compare time from hospital discharge, or first appointment for those outpatients who did not require hospitalization, to first suicidal event or the censoring point as appropriate with insight levels at baseline. Participants were censored as non-attempters at the time of the last face-to-face assessment with a member of staff. Unlike binary logistic regression, survival analyses capture the dynamics of suicide/non-suicide status which, indeed, can change over the course of the illness. For instance, a suicide attempt that occurs early should be accounted for differently from a later suicidal event. Equally, a non-suicide attempter who is lost to follow-up in an early phase should not be considered in the same way as those non-suicide attempters who completed the follow-up. This methodology was chosen to overcome the limitation from the vast majority of previous studies, which used logistic regression.

In addition, multivariable Mandel-Cox regression models (Cox, 1972) were built up in order to investigate survival in relation to baseline insight variables, whilst adjusting the analyses for potential mediating/confounding demographic and clinical variables.

All of the above analyses were two-tailed and significance level was set at 5%.

4.4.c.1. – Power calculations

I used the *stpower logrank* command of STATA 11.0 for Windows (StataCorp LP, USA) to conduct the power calculations pertaining to insight variables.

Thus, the FEP cohort presented in this chapter was followed-up over a period ranging from 3 to 6 years. Based on previous FEP studies, it is expected that at the end of the follow-up at least 20% of the initial sample size will have made one suicide attempt (e.g. Robinson et al., 2010), including 2-5% of suicides (Dutta et al., 2010; Palmer et al., 2005). Given that the mean SAI-E score for FEP patients is around 13/28 with a standard deviation of around 6 (e.g. Morgan et al., 2010), a difference of 2 points (e.g. 13 vs 15) between suicide attempters and non-attempters, which is considered to be clinically meaningful (Kemp & David, 1998), is

equivalent to an effect size of 0.33 with a two-tailed alpha set at 5%. Under these assumptions I will have 62.5% power to detect such 2-point difference in this sample (n=112).

4.5. – Results

4.5.a. – Baseline demographic and clinical characteristics of the sample

The sample comprised 112 GAP participants. The sociodemographic and clinical characteristics of the whole sample, including the number of patients with information available on each variable, and differences between those with/without suicide attempts (SA) prior to first presentation are presented in Tables 4.1 and Table 4.2 below.

Table 4.1. GAP: Baseline demographic and clinical characteristics of the sample and comparisons between patients with/without previous suicide attempts

	Data available N (%)	Total sample N=112	With previous SA n = 22 (19.6%)	Without previous SA n = 90 (80.3%)	Statistic	p-value
Age at first contact, years	112 (100)	29.4 ± 9.2	27.8 ± 5.8	29.8 ± 5.8	T = -1.2	0.21
Gender, males	112 (100)	73 (65.2)	13 (59.0)	60 (66.6)	X^2 = 0.5	0.50
Level of education	110 (98.2)					
No qualifications		18 (66.4)	4 (18.2)	14 (15.9)	X^2 = 0.1	0.79
GCSE		23 (20.9)	5 (22.7)	18 (20.4)	X^2 = 0.1	0.81
Further		42 (38.2)	7 (31.8)	35 (39.8)	X^2 = 0.5	0.50
University		27 (24.5)	6 (27.3)	21 (23.8)	X^2 = 0.1	0.74
Unmarried	111 (99.1)	84 (75.7)	16 (72.7)	68 (76.4)	X^2 = 0.1	0.72
Living alone	111 (99.1)	40 (36.0)	11 (50.0)	29 (32.5)	X^2 = 2.3	0.13
Unemployed	110 (98.2)	69 (62.7)	10 (45.4)	59 (67.0)	X^2 = 3.5	0.06
Ethnicity	111 (99.1)					
White		29 (26.1)	9 (40.9)	20 (22.5)	X^2 = 3.1	0.08
Black		49 (44.1)	6 (27.2)	43 (48.3)	X^2 = 3.2	0.07
Other		33 (29.7)	7 (31.8)	26 (29.2)	X^2 = 0.1	0.81
DUP: days, median	111 (99.1)	42	36	60	U	0.85
Diagnosis (ICD-10)	111 (99.1)					
Schizophrenia spectrum		86 (77.5)	15 (71.4)	71 (78.9)	X^2 = 0.5	0.46
Mania with psychosis		16 (14.4)	3 (14.3)	13 (14.4)	X^2 = 0.0	0.98
Psychotic depression		9 (8.1)	3 (14.3)	6 (6.6)	X^2 = 1.3	0.25
Cannabis use	89 (79.5)					
Use		81 (72.3)	18 (81.8)	63 (70.0)	X^2 = 1.2	0.27
Abuse/dependence		41 (46.1)	7 (38.9)	34 (47.9)	X^2 = 0.50	0.50
Alcohol	90 (80.3)					
Use		68 (75.6)	14 (87.5)	54 (72.9)	X^2 = 1.5	0.22
Abuse/dependence		29 (32.2)	6 (26.0)	23 (31.1)	X^2 = 0.2	0.62

GAP: Genetics and Psychosis Study. SA: suicide attempts (prior to first presentation).

4.5.b. – Insight

4.5.b.1. – Values and scores distribution

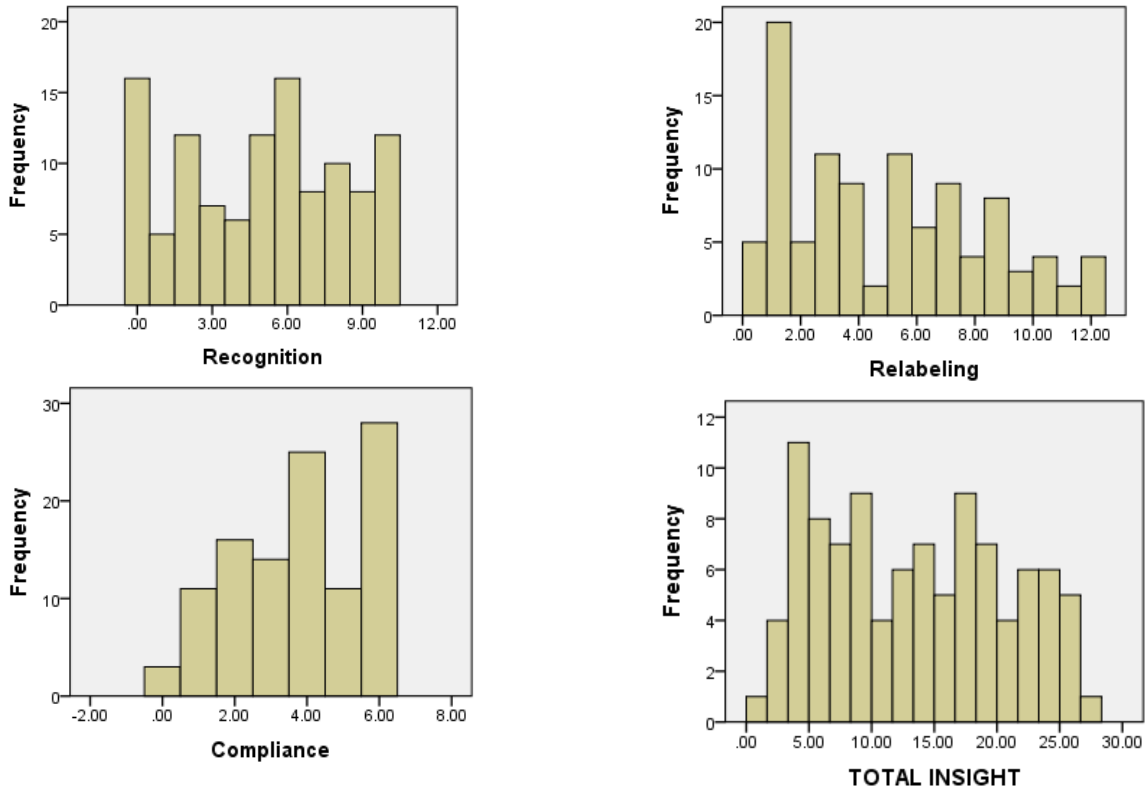
The insight total scores and insight dimensions levels are summarised in table 4.2. In particular, the mean, standard deviation (SD), median and range of scores for recognition of illness, symptoms relabeling, treatment compliance and the total insight are presented. Kolmogorov-Smirnov tests confirmed normal distribution for the insight scores except compliance, which was skewed towards better compliance but which resembled normality sufficiently (see figure 4.1 below) so parametric tests were used.

Table 4.2. Insight scores across the GAP sample

	Data available N (%)	**Mean ± SD**	**Median**	**Min - Max**	**K-S test**
Recognition	112 (100)	4.9 ± 3.3	5.0	0 – 10	0.11
Relabelling	103 (91.9)	4.9 ± 3.4	4.9	0 – 12	0.15
Compliance	108 (96.4)	3.7 ± 1.8	4.0	0 - 6	0.02
Total insight	100 (89.3)	13.6 ± 7.3	13.6	1 – 28	0.30

GAP: Genetics and Psychosis Study. SD: Standard deviation. K-S: Kolmogorov-Smirnov Test

Figure 4.1. Insight distributions across the GAP sample



GAP: Genetics and Psychosis Study

4.5.b.2. – Correlations between insight dimensions

All insight dimensions showed significant ($p<0.01$) and positive correlations between themselves. Recognition of illness and treatment compliance showed the weakest correlation ($r=0.42$), while relabelling and recognition had the strongest correlation ($r=0.75$). All these correlations are presented in table 4.3 below.

Table 4.3. GAP: Correlation matrix* of theoretical insight dimensions (N=112)

	Recognition	Relabelling	Compliance
Recognition		0.75	0.42
Relabelling	0.75		0.48
Compliance	0.42	0.48	

GAP: Genetics and Psychosis Study
*Pearson r coefficients, all significant at $p<0.01$ (two-tailed)

4.5.b.3. – Factor analysis

An exploratory factor analysis with Varimax rotation was performed in order to assess the degree of similarity between these data and the 3-factor model proposed by David (David, 1990). However, our factor analysis yielded two factors with eigenvalues over 1. These factors explained 47.4% and 12.9% of the variance, so in total 60.3% of the variance.

A separate factor analysis was conducted in which 3 factors were forcibly retained in keeping with previous studies (e.g. Morgan et al., 2010b). However, the solution that emerged was even less satisfactory than the 2-factor solution. Hence, the original 3-factor structure was not replicated in this sample. In particular, the 'relabelling' component did not emerge as an independent third factor and it was captured by the 'recognition' factor.

Table 4.4. GAP: Factor loadings following a varimax rotation on the SAI-E

	Rotated component Matrix*		
		Factors	
SAI-E item	**Insight dimensions**	**1**	**2**
1	Recognition	0.71	0.03
2		0.83	-0.00
3		0.76	0.19
4		0.80	0.07
5		0.72	0.09
6		0.54	0.51
7	Relabeling	0.80	0.13
8		0.73	0.30
9		0.60	0.25
10	Compliance	-0.03	0.86
11		0.17	0.77
Initial eigenvalues		**5.22**	**1.42**
Variance explained (%)		**47.4**	**12.9**

GAP: Genetics and Psychosis Study
Extraction Method: Principal Component Analysis
Rotation Method: Varimax with Kaiser Normalization
*Rotation converged in 3 iterations

4.5.c. – Differences between patients with/without previous suicide attempts in insight levels, psychopathology and neurocognitive variables

Illness recognition and symptoms relabeling were found to be significantly higher in those with SA before first presentation than in those subjects without such antecedents as detailed in table 4.5 below. In addition, the depression score was higher in the suicidal group than in those without such antecedents, although the difference only did not reach statistical significance ($p=0.08$). Also, there were no significant differences between groups in terms of neurocognitive variables.

Table 4.5. GAP: Differences in insight, psychopathology and neurocognitive variables between patients with/without previous suicide attempts

	Data availability n (%)	Total sample	With previous SA	Without previous SA	Statistic	p-value
Insight scores						
Recognition	**112 (100)**		**n=22**	**n=90**		
		4.9 ± 3.3	**6.2 ± 2.7**	**4.7 ± 3.3**	**t = 2.0**	**p=0.05**
Relabelling	**103 (91.9)**		**n=21**	**n=82**		
		4.9 ± 3.4	**6.4 ± 3.1**	**4.5 ± 3.4**	**t = 2.2**	**p=0.03**
Compliance	108 (96.4)		n=21	n=87		
		3.7 ± 1.8	4.3 ± 1.8	3.6 ± 1.8	t = 1.6	p=0.11
Total Insight	**100 (89.2)**		**n=20**	**n=80**		
		13.6 ± 7.3	**16.8 ± 6.4**	**12.8 ± 7.4**	**t = 2.2**	**p=0.03**
Psychopathology	*109 (97.3)*		*n=21*	*n=88*		
Positive		9.2 ± 4.4	8.7 ± 4.3	9.3 ± 4.4	U	0.47
Negative		11.9 ± 6.1	12.0 ± 5.6	11.9 ± 6.2	U	0.95
Disorganization		6.4 ± 2.7	5.5 ± 2.3	6.6 ± 2.8	U	0.37
Mania		5.4 ± 2.2	4.8 ± 1.1	5.5 ± 2.4	U	0.98
Depression		7.2 ± 3.2	8.3 ± 3.5	6.9 ± 3.0	t = 1.7	0.08
Premorbid IQ	*90 (80.3)*		*n=18*	*n=72*		
Verbal		87.9 ± 11.3	88.9 ± 11.1	87.7 ± 11.4	t = 0.4	0.67
Performance		94.7 ± 10.6	96.5 ± 7.2	94.3 ± 11.3	t = 0.8	0.42
Full		90.5 ± 10.6	91.9 ± 9.6	90.1 ± 10.8	t = 0.6	0.52
IQ (WAIS-III)	*92 (82.1)*		*n=18*	*n=74*		
		88.4 ± 25.3	93.9 ± 14.1	87.1 ± 27.3	t = 1.0	0.31
TMT-A (seconds)	*92 (82.1)*		*n=18*	*n=74*		
		47.0 ± 20.9	41.6 ± 17.1	48.3 ± 21.7	t = -1.2	0.23
TMT-B (seconds)	*86 (76.8)*		*n=18*	*n=68*		
		119.5 ± 74.0	97.7 ± 56.1	125.2 ± 77.4	t = -1.4	0.16
TMT-B-A (seconds)	*86 (76.8)*		*n=18*	*n=68*		
		71.8 ± 62.4	60.3 ± 49.6	74.8 ± 65.4	t = -0.8	0.38

GAP: Genetics and Pychosis Study. SA: Suicide attempts (prior to first presentation/contact) IQ: Intelligence Quotient. WAIS-III: Wechsle Adult Intelligence Scale Revised (Wechsler, 1981). TMT: Trail Making test (Reitan, 1958).

4.5.d. – Bivariate analyses: relationships between insight dimensions and baseline demographic and clinical characteristics of the sample

I performed exploratory analyses in order to investigate potential relationships between insight levels and a set of demographic variables, such as age at first contact, gender, education level, marital, living and employment status and ethnicity. However, only gender and ethnicity revealed significant differences in insight levels. In particular, females showed a higher level of recognition (6.0 ± 3.2 vs. 4.4 ± 3.2, p=0.01) and total insight (15.9 ± 7.1 vs. 12.4 ± 7.3, p=0.02) than males and those of White ethnicity had significantly higher levels of compliance than the two remaining groups, i.e. Black people and 'other ethnicity' (4.5 ± 1.7 vs. 3.5 ± 1.7, p=0.04). Further non-significant differences are detailed in table 4.6 below.

Table 4.6. GAP: Baseline demographic data and insight levels

	Recognition	Relabelling	Compliance	Total insight
Age at first contact	n = 112	n = 103	n = 108	n = 100
	r=-0.09	r = -0.13	r = -0.04	r =-0.08
	p=0.32	r = 0.17	p = 0.63	p = 0.15
Gender	**n = 112**	n = 103	n = 108	**n = 100**
Males	**4.4 ± 3.2**	4.6 ± 3.2	3.6 ± 1.8	**12.4 ± 7.3**
Females	**6.0 ± 3.2**	5.6 ± 3.7	4.1 ± 1.7	**15.9 ± 7.1**
	t=-2.4, p=0.01	t=-1.4, p=0.15	t=-1.4, p=0.16	**t=-2.3, p=0.02**
Level of education	n=110	n=101	n=106	n=98
No qualifications	3.9 ± 2.9	4.1 ± 3.1	4.1 ± 1.8	11.6 ± 6.8
≥ GCSE	5.2 ± 3.3	5.0 ± 3.4	3.7 ± 1.8	14.0 ± 7.4
	t=-1.5, p=0.15	t=-1.0, p=0.31	t=0.7, p=0.48	t=-1.2, p=0.23
Marital status	n=111	n=102	n=107	n=99
Unmarried	4.8 ± 3.4	4.7 ± 3.4	3.7 ± 1.8	13.2 ± 7.5
Married	5.3 ± 2.9	5.5 ± 3.5	3.8 ± 1.7	14.6 ± 6.5
	t=-0.7, p=0.47	t=-0.99, p=0.32	t=-0.1, p=0.89	t=-0.7, p=0.43
Living status	n=111	n=102	n=107	n=99
Alone	5.2 ± 3.4	5.2 ± 3.4	3.6 ± 1.8	14.0 ± 7.7
With others	4.8 ± 3.2	4.7 ± 3.4	3.8 ± 1.7	13.2 ± 7.1
	t=0.7, p=0.45	t=0.7, p=0.48	t=-0.6, p=0.52	t=-0.5, p=0.60
Employment status	n=111	**n=102**	n=107	**n=99**
Unemployed	4.6 ± 6.3	**4.4 ± 3.3**	3.5 ± 1.7	**12.4 ± 7.2**
Employed	5.5 ± 3.2	**5.9 ± 3.4**	4.2 ± 1.8	**15.6 ± 7.1**
	t=-1.5, p=0.14	**t=-2.2, p=0.03**	t=-1.9, p=0.06	**t=-2.1, p=0.04**
Ethnicity	n=111	n=102	n=107	n=99
White	6.6 ± 3.2	6.2 ± 3.5	**4.5 ± 1.7***	16.5 ± 7.7
Black	4.4 ± 3.2	4.2 ± 3.0	**3.5 ± 1.7**	12.4 ± 6.5
Others	4.7 ± 3.3	4.9 ± 3.6	**3.5 ± 1.8**	13.1 ± 7.9
	F=2.4, p=0.09	F=2.7, p=0.06	**F=3.4, p=0.04**	F=2.6, p=0.08

GAP: Genetics and Psychosis Study. GCSE: General Certificate of Secondary Education.

With regard to baseline clinical characteristics of the sample such as DUP, diagnosis and alcohol and illicit drugs use/abuse/dependence, several significant differences emerged from the bivariate analyses which are shown in table 4.7 below.

DUP was dichotomised into two groups by splitting the sample through the median since the distribution of DUP values was skewed. Thus, all insight scores were significantly lower in those with a long (>42 days) DUP, i.e. the longer the DUP, the poorer the insight.

In terms of diagnosis, those subjects with psychotic depression showed significantly greater levels of insight than those with schizophrenia spectrum disorders and mania with psychosis.

In addition, drugs users were found to have greater levels of illness recognition and symptom relabelling than those who never took illicit drugs.

Other non-significant differences are presented in table 4.7 below.

Table 4.7. GAP: Baseline clinical characteristics and insight dimensions

	Recognition	Relabelling	Compliance	Total Insight
DUP	***n=111***	***n=102***	***n=107***	***n=99***
< 42 days	**5.5 ± 3.1**	**5.8 ± 3.2**	**4.1 ± 1.6**	**15.4 ± 6.7**
> 42 days	**4.3 ± 3.3**	**4.0 ± 3.3**	**3.4 ± 1.8**	**11.7 ± 7.4**
	t=-2.0, p=0.04	**t=-2.6, p<0.01**	**t=-2.2, p=0.03**	**t=-2.6, p=0.01**
Diagnosis	***n=111***	***n=102***	***n=108***	***n=100***
Schizophrenia	**4.6 ± 3.3**	**4.7 ± 3.2**	**3.8 ± 1.8**	**13.1 ± 7.0**
Mania	**4.5 ± 3.2**	**4.0 ± 3.6**	**3.0 ± 1.8**	**11.3 ± 7.7**
Depression*	**8.8 ± 1.1**	**8.7 ± 2.7**	**5.2 ± 0.9**	**22.8 ± 3.4**
	F=7.5, p<0.01	**F=6.3, p<0.01**	**F=4.6, p=0.01**	**F=8.1, p<0.01**
Alcohol	*n=90*	*n=86*	*n=87*	*n=84*
Use	5.5 ± 3.3	5.4 ± 3.6	4.0 ± 1.8	14.9 ± 7.4
non-use	4.4 ± 2.5	4.2 ± 2.6	3.6 ± 1.8	11.9 ± 5.9
	t=1.5, p=0.13	t=1.6, p=0.11	t=0.9, p=0.36	t=1.6, p=0.10
Abuse/dep	5.7 ± 3.2	5.9 ± 3.2	4.2 ± 1.6	15.8 ± 7.3
non-abuse/dep	5.0 ± 3.1	4.7 ± 3.4	3.8 ± 1.8	13.4 ± 7.1
	t=0.9, p=0.32	t=1.6, p=0.10	t=1.2, p=0.23	t=1.4, p=0.17
Drugs	***n=112***	***n=103***	*n=108*	*n=100*
Use	**5.4 ± 3.2**	**5.4 ± 3.5**	3.8 ± 1.8	14.5 ± 7.5
non-use	**3.9 ± 3.1**	**3.7 ± 2.9**	3.7 ± 1.6	11.4 ± 6.6
	t=2.3, p=0.02	**t=2.2, p=0.02**	t=0.4, p=0.69	t=1.9, p=0.06
Abuse	5.3 ± 3.6	5.6 ± 3.4	3.9 ± 1.8	15.0 ± 7.9
non-abuse/dep	5.0 ± 3.2	4.9 ± 3.6	3.8 ± 1.9	13.4 ± 7.6
	t=0.3, p=0.73	t=0.8, p=0.40	t=0.4, p=0.69	t=0.9, p=0.36

GAP: Genetics and Psychosis Study. DUP: Duration of untreated psychosis

I also conducted correlation analyses between insight scores and psychopathological dimensions and neurocognitive variables, which are detailed in table 4.8 below, and revealed several significant differences. With regard to psychopathology, disorganization correlated negatively with all insight scores except compliance ($p<0.01$), while mania showed negative significant correlations with the four insight scores.

Interestingly, depression showed very significant positive correlations with all insight dimensions ($p<0.01$) except compliance, which correlated positively with negative symptoms ($r=0.22$, $p=0.03$) and negatively with mania ($r=-0.21$, $p=0.03$). Finally, full premorbid IQ showed a positive significant correlation with recognition ($r=0.22$, $p=0.03$) and TMT-B was significantly associated with recognition (r-0.21, $p=0.04$) and relabeling ($r=-0.26$, $p=0.02$), i.e. the longer it takes to complete the task, the poorer the executive functions performance.

Table 4.8. GAP: Correlations between insight levels, psychopathology measures and cognition

	Recognition			Relabelling			Compliance			Total Insight		
	n	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**
Positive	**109**	**-0.25**	**0.01**	**101**	**-0.28**	**0.01**	105	-0.08	0.41	**98**	**-0.24**	**0.01**
Negative	109	-0.00	0.96	101	0.06	0.53	**105**	**0.22**	**0.03**	98	0.10	0.35
Disorganization	**108**	**-0.33**	**<0.01**	**100**	**-0.28**	**<0.01**	104	-0.05	0.61	**97**	**-0.28**	**<0.01**
Mania	**109**	**-0.21**	**0.03**	**101**	**-0.26**	**0.01**	**105**	**-0.21**	**0.03**	**98**	**-0.24**	**0.02**
Depression	**109**	**0.32**	**<0.01**	**101**	**0.27**	**0.01**	105	0.17	0.08	**98**	**0.33**	**<0.01**
Premorbid IQ	**90**	**0.22**	**0.03**	85	0.18	0.09	87	-0.00	0.96	83	0.14	0.19
IQ (WAIS-III)	92	0.09	0.39	86	0.11	0.29	89	0.03	0.75	84	0.07	0.53
TMT-A (seconds)	92	-0.18	0.07	86	-0.13	0.24	89	0.02	0.84	84	-0.13	0.24
TMT-B (seconds)	**86**	**-0.21**	**0.04**	**81**	**-0.26**	**0.02**	83	0.00	0.99	79	-0.19	0.08
TMT B-A (seconds)	86	-0.16	0.15	81	-0.20	0.07	83	0.00	0.95	79	-0.15	0.20

GAP: Genetics and Psychosis Study. IQ: Intelligence Quotient. WAIS: Wechsler Adult Revised Intelligence Scale (Wechsler, 1981). TMT: Trail Making Test (Reitan, 1958)

4.5.e. – Regression on recognition of illness

A hierarchical linear regression model (by using 'enter' method, i.e. all the variables were initially entered the model) was carried out to reassess the association of previous SA with illness recognition after controlling for gender, ethnicity, DUP, diagnosis of 'psychotic depression' and drugs use. In addition, I included two more blocks of variables into the model with those neurocognitive and psychopathological variables which had emerged significant from the bivariate analyses to determine predictors of illness recognition. Thus, only a diagnosis of depression remained significant ($p<0.01$), while disorganization showed a trend ($p=0.08$). This model explained 38% of the variance on recognition.

Table 4.9. GAP: Regression on recognition

	B	SE	p	R^2 Change	p-change
Block 1:				*0.084*	*0.03*
Gender	-0.76	0.66	0.26		
White	0.58	0.76	0.44		
Block 2:				*0.038*	*0.07*
DUP (> 42 days)	-0.98	0.61	0.11		
Block 3:				*0.122*	*<0.01*
Depression (dx)	2.7	1.1	0.01		
Block 4:				*0.044*	*0.04*
Drugs	1.23	0.74	0.10		
Block 5:				*0.003*	*0.57*
Suicidal history	0.12	0.72	0.86		
Block 6:				*0.012*	*0.56*
Full premorbid IQ	0.02	0.03	0.59		
TMT-B	0.00	0.01	0.46		
Block 7:				*0.075*	*0.10*
Positive	-0.05	0.08	0.55		
Disorganization	-0.23	0.13	0.08		
Mania	-0.07	0.18	0.70		
Depression	0.19	0.12	0.11		
GLOBAL R^2				0.38	

GAP: Genetics and Psychosis Study. DUP: Duration of untreated psychosis. dx: diagnosis.
IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

4.5.f. – Regression on relabelling of symptoms

A hierarchical linear regression model (by using 'enter' method as explained above) was carried out to reassess the association of previous SA with symptoms relabelling after controlling for the effects of unemployment, DUP, diagnosis of 'psychotic depression' and drugs use, since they all were significantly associated with relabelling in the bivariate analyses. I also added two more blocks of variables to the model with those neurocognitive and psychopathological linked with relabelling. DUP (p=0.02), a diagnosis of depression (p<0.01) and drugs use (p=0.04) survived as significant predictors of relabelling. This final model accounted for 31% of the variance on relabelling of symptoms.

Table 4.10. GAP: Regression on relabelling

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				*0.031*	*0.13*
Unemployment	-1.25	0.74	0.09		
Block 2:				*0.068*	*0.02*
DUP (> 42 days)	-1.67	0.70	0.02		
Block 3:				*0.170*	*<0.01*
Depression (dx)	4.61	1.27	<0.01		
Block 4:				*0.069*	*<0.01*
Drugs	1.74	0.82	0.04		
Block 5:				*0.000*	*0.85*
Suicidal history	-0.10	0.88	0.902		
Block 6:				*0.002*	*0.66*
TMT-B	-0.00	0.00	0.74		
Block 7:				*0.039*	*0.40*
Positive	0.02	0.08	0.79		
Disorganization	-0.16	0.09	0.11		
Mania	-0.09	0.20	0.65		
Depression	0.11	0.13	0.42		
GLOBAL R^2				0.31	

GAP: Genetics and Psychosis Study. DUP: Duration of untreated psychosis. dx: diagnosis.
IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

4.5.g. – Regression on treatment compliance

A hierarchical linear regression model (which used 'enter' method) was carried out to assess potential predictors of treatment compliance. Since the relationship between suicidality and compliance had not reached significance, suicidal history was not included into the model. Thus, being white (p=0.02), DUP (p=0.04), a diagnosis of psychotic depression (p<0.01) and manic symptoms severity (p=0.03) predicted compliance, although the model only explained a 22% of the variance on this insight domain.

Table 4.11. GAP: Regression on compliance

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				*0.055*	*0.02*
White	0.83	0.37	0.02		
Block 2:				*0.044*	*0.03*
DUP (> 42 days)	-0.67	0.32	0.04		
Block 3:				*0.065*	*<0.01*
Depression (dx)	1.39	0.57	0.02		
Block 4:				*0.054*	*0.04*
Negative	0.03	0.03	0.20		
Mania	-0.15	0.07	0.03		
GLOBAL R^2				0.22	

GAP: Genetics and Psychosis Study. DUP: Duration of untreated psychosis. dx: diagnosis

4.5.h. – Regression on total insight

A hierarchical linear regression model (by using 'enter' method) was carried out to reassess the association of previous SA with total insight after controlling for the effects of gender, unemployment, DUP, diagnosis of 'psychotic depression' and several psychopathological dimensions such as positive, disorganization, mania and depression, which all had been associated with total insight. In addition, in order to determine the predictors of recognition of illness, I included one more block with three psychopathological dimensions such as disorganization, mania and depression into the model. Thus, DUP (p=0.03) and a diagnosis of depression (p<0.01) emerged as significant predictors of total insight. In particular, this model accounted for up to 31% of the variance on total insight.

Table 4.12. GAP: Regression on total insight

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				*0.087*	*0.01*
Gender	-1.23	1.40	0.36		
Unemployment	-1.41	1.39	0.31		
Block 2:				*0.064*	*0.01*
DUP	-2.89	1.31	0.03		
Block 3:				*0.110*	*<0.01*
Depression (dx)	7.28	2.47	<0.01		
Block 4:				*0.012*	*0.23*
Previous SA	-1.05	1.66	0.53		
Block 5:				*0.040*	*0.30*
Positive	-0.04	0.17	0.80		
Disorganization	-0.36	0.27	0.19		
Mania	-0.26	0.32	0.42		
Depression	0.17	0.22	0.44		
GLOBAL R^2				0.31	

GAP: Genetics and Psychosis Study.dx: diagnosis. SA: suicide attempts (before first contact)

4.5.i. – Suicidal behaviours over the 3-year follow-up period

In total, 32 subjects (28.5%) made at least one suicide attempt either prior to first contact with services or over the follow-up. Eighteen individuals (16.1%) attempted to take their lives over the follow-up, 8 of whom (7.1%) did so both before and after first presentation to services. 6 patients made two suicide attempts over the follow-up period and 3 subjects died from suicide over the 3-year that period, which yielded a case fatality of 3/112=2.7%. This is summarized in figure 4.2.

In particular, 18 follow-up suicide attempters, including 3 suicide completers, and 94 non-suicide attempters were compared through Kaplan-Meier survival analyses and Cox Regression models with regard to baseline insight levels, whilst adjusting the analyses for a set of demographic and clinical variables. Of note, the median time from first contact to first suicide attempt was 1 year, as shown by the Kaplan-Meier Curve below (Figure 4.2.).

Also, most of the suicidal acts occurred shortly after the last appointment with a SLaM member of the staff. The median of this time was 8 days for the first attempt (n=18) and 6.5 days for the second attempt (n=6). Also, the three suicides occurred within 10 days, 17 days and almost three months after last face-to-face contact with the staff, respectively.

Figure 4.1. Kaplan-Meier Survival Curve showing time to first suicide attempt over the follow-up period in suicide attempters and completers, n=18

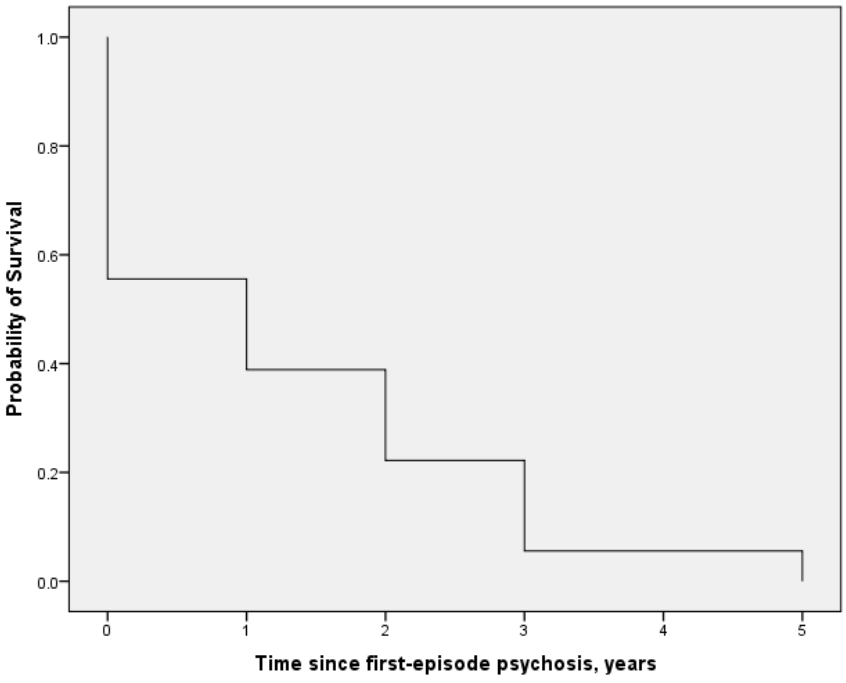
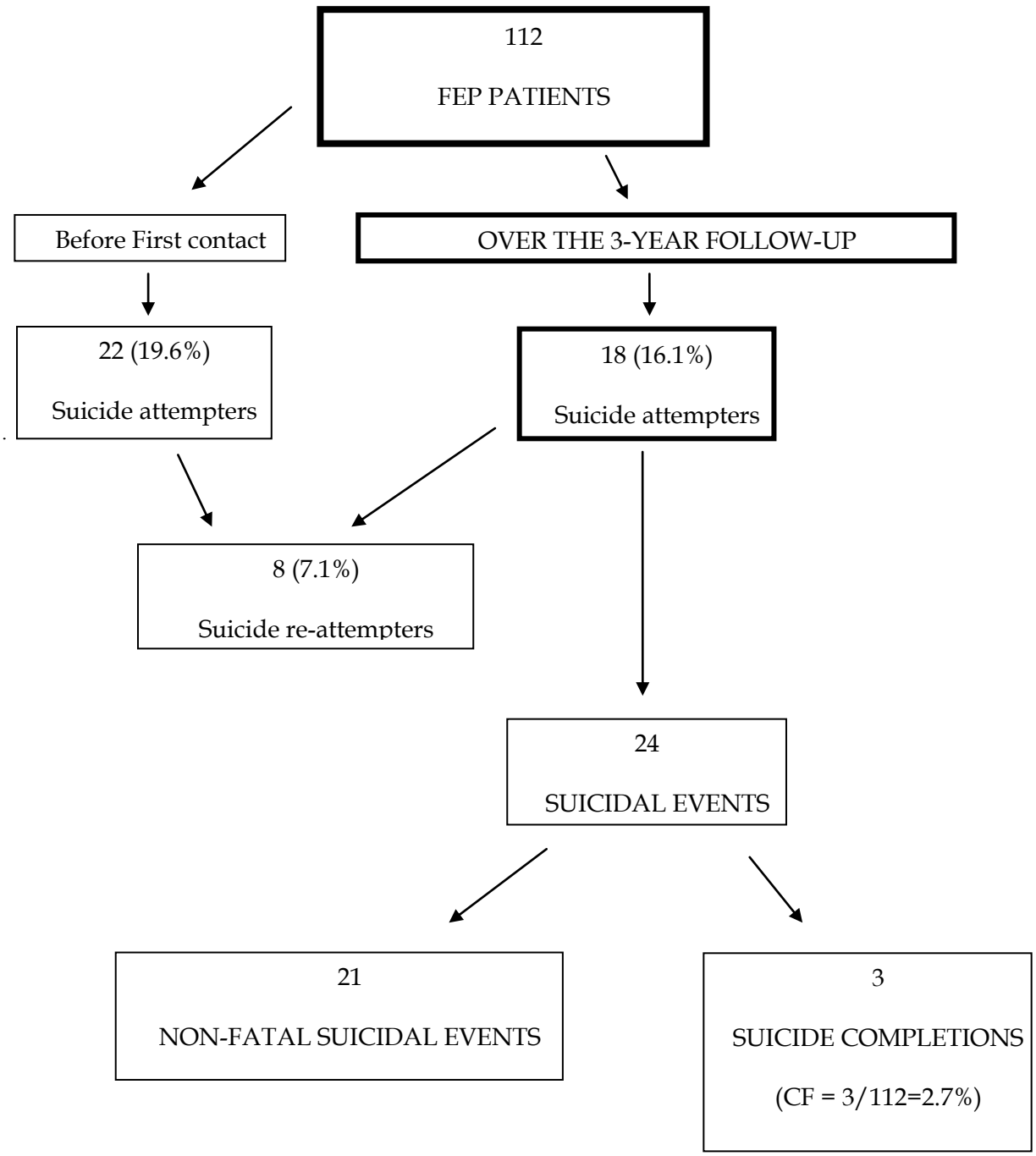


Figure 4.2. Flow chart of suicidal events in the GAP study



GAP: Genetics and Psychosis Study. FEP: First-episode psychosis. CF: case-fatality

4.5.j. – Suicide methods

As detailed in figure 4.4., above, there were 24 suicidal events over the follow-up. Thus, poisoning (n=10) and cutting (n=6) were the most common suicide methods. Also, there were suicide attempts by violent methods such as jumping (n=4), which included jumping from a height or in front of a train. There were no suicide attempts by firearms.

Also, 3 subjects ended their lives, who were all males. One suicide completer with bipolar affective disorder was found dead at home after taking an overdose of medication within the context of a depressive relapse. Another individual, who suffered from schizophrenia, set fire at his home two weeks after disengaging from the team and possibly discontinuing medication. Finally, one subject jumped from a height locally.

Table 4.13. GAP: Suicide methods

Method	Events (n=24)
Poisoning*	10
Cutting him/herself	8
Jumping*	4
Hanging	1
Setting a fire*	1

GAP: Genetics and Psychosis Study
*one suicide completion each by this method

4.5.k. – Risk factors for suicidal behaviour over the follow-up

Univariate analyses concerning demographic, clinical and symptom-related variables, including insight, are presented below in tables 4.14, 4.15 and 4.16, respectively.

Table 4.14. GAP: Univariate analysis: log-rank tests of equality of survival distributions for the demographic variables

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Gender	Male	11.7	12	0.03	0.86
	Female	6.3	6		
Age at first contact	**<28**	**9.8**	**14**	**4.01**	**0.04**
	>28	**8.2**	**4**		
Education level	No qualifications	2.8	4	1.58	0.66
	GCSE	3.5	4		
	Higher	6.5	7		
	University	4.2	2		
Marital status	Unmarried	12.9	14	0.49	0.48
	Married	4.1	3		
Living status	**Alone**	**6.1**	**11**	**4.46**	**<0.01**
	Not alone	**10.9**	**6**		
Employment status	Unemployed	10.7	9	1.01	0.32
	Employed	6.3	8		
Ethnicity	White	4.4	7	2.34	0.31
	Black	7.5	6		
	Other	5.0	4		

GAP: Genetics and Psychosis Study. GCSE: General Certificate of Secondary Education

Table 4.15. GAP: Univariate analysis: log-rank tests of equality of survival distributions for the clinical variables

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Previous SA	**Absent**	**14.5**	**10**	**10.06**	**<0.01**
	Present	**3.5**	**8**		
DUP	<42	8.6	10	0.72	0.40
	>42	8.4	7		
Diagnosis	Schizophrenia	13.9	17	3.24	0.19
	Mania	2.5	1		
	Depression	1.4	0		
Drugs use	Absent	4.9	3	0.98	0.32
	Present	13.0	15		
Alcohol use	Absent	3.2	2	0.97	0.32
	Present	9.8	13		

GAP: Genetics and Psychosis Study. SA: Suicide attempts (before first contact).
DUP: Duration of untreated psychosis.

Table 4.16. GAP: Cox regression analyses for neurocognitive, psychopathological and insight-related variables

Risk factor	RR	95% CI	p-value
Neurocognition			
Full premorbid IQ	0.95	0.91 - 1.00	0.09
TMT-B-A	0.83	0.99 – 1.01	0.83
Psychopathology			
Positive	1.02	0.91 – 1.15	0.70
Negative	1.06	0.99 – 1.14	0.10
Disorganization	0.98	0.82 – 1.17	0.83
Mania	0.83	0.59 – 1.16	0.20
Depression	1.07	0.92 – 1.14	0.37
Insight			
Recognition of illness	1.09	0.94 – 1.26	0.24
Symptoms relabeling	1.10	0.95 - 1.26	0.19
Treatment compliance	**1.36**	**1.01 – 1.83**	**0.04**
Total insight	1.06	0.99 – 1.14	0.08

GAP: Genetics and Psychosis Study. RR: Relative Risk. CI: Confidence Interval. IQ: Intelligence Quotient.
TMT B-A: Trail Making Test, time to complete task B minus time to complete task A (Reitan, 1958)

Age at first presentation, which was dichotomised through the median (28 years) (RR 2.92, 95% CI 0.96-8.86, p=0.06), living alone (RR 3.57, 95% CI 1.32-9.65, p=0.01), suicidal history (RR 3.95, 95% CI 1.55-10.1, p<0.01), premorbid IQ (RR 0.96, 95% CI 0.91-1.01, p=0.09), treatment compliance (RR 1.06, 95% CI 1.01-1.83, p=0.04), and total insight (RR 1.06, 95% CI 0.99-1.14, p=0.08) were most strongly related to risk of suicidal behaviour. Of note, no psychopathological dimension, including depression, was significantly associated with risk of suicidal behaviours over the follow-up.

Therefore, young age at first presentation (<28 years), living status (i.e. living alone) suicidal history, premorbid IQ, treatment compliance and total insight were entered into the first forward stepwise Cox regression model. Living alone (RR 3.24, 95% CI 1.04-10.04, p=0.04) and suicidal history (RR 7.36, 95% CI 2.25-24.04, p<0.01) remained significant as shown in table 4.17. below.

Table 4.17. GAP: Multivariate analysis: Risk factors for suicidal behaviour from Cox regression modelling

Risk factor		RR	95% CI	p-value
Living status	**Alone**	**3.24**	**1.04 – 10.04**	**0.04**
	Not alone	**1.00**		
Previous SA	**Present**	**7.36**	**2.25 – 24.04**	**<0.01**
	Absent	**1.00**		

Model based on n=82 GAP patients, including 13 suicide attempters, whom had complete data for all the variables in the model
GAP: Genetics and Psychosis Study. RR: Relative Risk. CI: Confidence Interval
SA: Suicide attempts (prior to first presentation/contact)

4.6. – Discussion

4.6.a. – Main findings

Two major conclusions can be drawn from the results presented in this chapter.

First, all insight dimensions except compliance were associated with a history of suicide attempts prior to first contact with services. However, other variables such as being white and unemployed, DUP, two psychopathological domains such as disorganization and mania symptoms severity (negatively) and a diagnosis of psychotic depression (as opposed to other psychoses), influenced insight levels at that time and thus mediate the above associations.

Second, although in contrast to my expectations the bivariate Kaplan-Meier analyses revealed treatment compliance and total insight to be linked with risk of suicidal behaviour over the follow-up, the multivariable Cox regression analyses showed that only living alone and a previous suicidal history predicted suicide risk, hence consistent with my hypothesis H5 concerning the role of mediating variables (see chapter 2, section 2.5). In addition, premorbid IQ and age at first presentation reduced suicide risk, although these variables did not survive the multivariable regression models.

4.6.b. – Insight levels at baseline are influenced by suicidal antecedents

As postulated, the bivariate analyses showed that all insight dimensions except treatment compliance were associated with suicidal history preceding first presentation with psychosis. However, contrary to my expectations these associations did not survive the multivariable regression models. A potential explanation may have been a lack of sufficient statistical power to test this. Alternatively, the above relationships may be mediated by other variables, which were related to insight and suicidal history, namely gender (female), unemployment, DUP and a diagnosis of psychotic depression (as opposed to other psychoses). Also, these variables were associated with suicidal history at a non-significant level, which may have been due to the limited statistical power.

The insight dimensions awareness/recognition of disorder and relabeling did not emerge as distinct factors in this sample, whereas compliance was less strongly correlated with the other two. Nevertheless, each insight dimension was associated with different predictors and correlates, which provides some support for the multidimensional model of insight (David, 1990; Amador & David, 2004).

With regard to gender and insight, several previous studies do not report differences (Markova, 2005), although in line with our results, those that do, tend to show that females have greater insight than males (Wiffen et al., 2012; Mintz et al., 2003; Parellada et al., 2011; McEvoy et al., 2006). Other socio-demographic variables such as age and level of education did not predict insight in our sample, although previous studies did find significant associations (Markova, 2005), particularly regarding education level (Wiffen et al., 2010), although white people showed higher levels of recognition and compliance, which is consistent with previous literature (Morgan, 2003; Goldberg et al., 2001; Johnson & Orrell, 1995). Unemployment was also associated with poorer ability to recall symptoms as pathological, including lower total insight scores, than employed patients. However, two previous studies showed no differences in insight according to employment status (Lysaker & Bell, 1994; David et al., 1995).

Of relevance to my main research question, I replicated the controversial association of depressive symptoms severity with two insight domains (illness recognition and symptom relabeling), and also with total insight (Peralta et al., 1998; Mintz et al., 2003; Cooke et al., 2005; Lincoln et al., 2007; Nair et al., 2014; Belvederi-Murri et al., 2015). However, the cross-sectional design does not allow causality conclusions to be drawn from this. In addition, three further psychopathological domains such as positive, disorganization and mania showed an inverse relationship with insight levels at first contact with services, which is in full agreement with a previous meta-analysis (Mintz et al., 2003). Also, compliance was (inversely) related to mania. Of interest, a positive relationship between compliance and negative symptom severity was revealed by the analyses, which suggests that (passive) compliance does not necessarily equate to awareness of illness (for a conceptual review, see Morgan & David, 2010).

Interestingly, those patients without suicidal antecedents were found to present with more severe depressive symptoms and greater levels of insight. Hence, it seems that based on our cross-sectional analyses one may intuitively conclude that insight is a risk factor for suicidal behaviour in early psychosis. However, as alluded to in chapter 2, such a conclusion would be subject to selection bias since the outcome variable (suicidal history) would precede the cause (insight), thus not fulfilling the causality criteria, particularly that of temporality (Hill, 1965).

Regarding DUP, an inverse relationship between insight and DUP was replicated (Pek et al., 2006; Saravanan et al., 2010; Cuesta et al., 2011), i.e. the longer the DUP, the poorer the insight at first presentation. However, the direction of causality remains unclear since it is

plausible that poor insight leads to avoidance of care and hence increases DUP (Drake et al., 2000) as it is that as DUP increases insight levels fall. Moreover, DUP was shorter (although not significantly) in the suicidal group in comparison with non-suicidal patients (Table 4.13), which suggests that suicidal behaviour shortens DUP by bringing the patient to the attention of psychiatric services earlier and subsequently, suicidality might increase insight at the point a FEP is diagnosed by lessening the negative effect of a more prolonged DUP on insight levels.

In contrast to previous extensive literature on 'insight and neurocognitive deficits in schizophrenia' (Amador et al., 1991; Morgan & David, 2004; Aleman et al., 2006; Ayesa-Arriola et al., 2011; David et al., 2012; Nair et al., 2014), the multivariate analyses failed to replicate a link between insight dimensions and two measures of cognition such as premorbid IQ and the TMT B-A, which assesses executive functions. However, these negative results were consistent with some previous studies (Cuesta et al., 1995; Ayesa-Arriola et al., 2014). Also, a previous analysis with an overlapping sample found verbal memory, which was not evaluated in this chapter, to predict insight above and beyond the effect of IQ (Wiffen et al., 2012).

4.6.c. – Insight dimensions did not predict suicide risk over the follow-up

Interestingly, in contrast to my hypotheses H5 and H6 (chapter 2, section 2.5.), awareness of the need for treatment was found to be a suicide risk factor over the 3-year follow-up period and total insight showed a borderline significance. However, no insight score predicted suicide risk over the follow-up period according to the multivariable Cox-regression models, consistent with my hypotheses outlined in chapter 2 (section 2.5). Therefore, there is a complex tautological issue here. First, suicidal history, which is the strongest predictor of future suicidal events in subjects with psychotic disorders (e.g. Hawton et al., 2005; Challis et al., 2013), affected insight levels at first presentation. Second, the bivariate analyses from the follow-up data found a link between insight at baseline and risk of suicidal behaviours over the 3-year follow-up; however, such an association did not remain significant after adjusting for previous suicidal history.

These findings concerning the lack of association of insight levels with suicide risk in early stages of psychosis were in line with my hypotheses (Chapter 2, section 2.5), my literature review (Lopez-Morinigo et al., 2012) and recent studies (Yan et al., 2013; Pijnenborg et al., 2013; Barrett et al., 2015), although many clinicians remain concerned about the risks associated with improving insight in patients with early onset psychosis.

However, I did replicate a relationship between insight, particularly illness recognition, and depression, as measured by the PANSS factor. This cross-sectional association again does not permit me to infer the direction of causality. Thus, although it is intuitive to believe that gaining awareness of suffering from such a serious illness leads to a depressive state, including an increased suicide risk, which is known as the 'demoralization syndrome' (Drake et al., 1985; Drake & Cotton, 1986; Amador et al., 1996; Restifo et al., 2009); equally, the so-called 'depressive realism model' may explain how a more depressed patient, biased by depression-related cognitions, loses their 'normal' optimistic biases and sees their illness for what it is (Ghaemi & Rosenquist, 2004), thus displaying higher levels of insight at the time of the assessment. This 'chicken and egg' dilemma can only be solved with longitudinal intervention studies; for example, if it was shown that insight improving interventions reduced suicidality. As alluded to above, intervention studies do not appear to suggest that improving insight increases suicidality (Pijnenborg et al., 2013), which is discussed further in chapter 8.

While the above overall negative results concerning the lack of association between insight dimensions and risk of suicidal behaviours were consistent with my hypotheses, they could also be attributed to the limited statistical power of these data as detailed in section 4.4.c.1. above.

4.6.d. – Predictors of suicidal behaviour over the follow-up

In addition to treatment compliance, three further predictors of suicidal behaviour over the follow-up emerged from the bivariate analyses, namely age at first contact, living alone and a previous suicidal history. However, only living alone and suicidal history remained significant in the multivariable Cox-regression model.

The inverse association of age with suicide risk in psychosis is one of the most consistent findings in the literature on the subject (e.g. Tsuang, 1978; Osby et al., 2000; Qin & Nordentoft, 2005; Palmer et al., 2005; Limosin et al., 2007; Osborn et al., 2008; Alaräisänen et al., 2009; Dutta et al., 2010; Barrett et al., 2010a; Barrett et al., 2010b), which suggests that close monitoring is needed in early stages of the psychotic illness (Popovic et al., 2014; NCISH, 2015). In keeping with this, early intervention services have been reported to reduce suicide risk in psychosis (Chan et al., 2014). Again, the lack of association of early age at first contact with services and suicide risk in the multivariate analyses may be explained by the limited statistical power of this study.

Living alone has been consistently found to be a risk factor for suicide both in schizophrenia (Hawton et al., 2005a) and FEP (Challis et al., 2013). A number of people with psychosis live alone in our catchment area (Kirkbride et al., 2006). To my knowledge, no previous FEP studies have examined whether transferring these patients to sheltered or supported accommodation, which tends to occur at late stages of the illness, in which suicide risk is lower than at earlier stages, although still significantly higher than in the general population (Dutta et al., 2010), reduces suicide risk. In keeping with this, being unmarried increased risk of suicidal behaviour over the follow-up period, although this difference did not reach significance, which was probably due to the small percentage of married patients in the sample (less than a quarter of the total sample). This finding is consistent with previous meta-analyses on both schizophrenia (Hawton et al., 2005) and FEP (Challis et al., 2013) which reported overall inconclusive results regarding the relationship between marital status and risk of suicide and deliberate self-harm, respectively.

In addition, suicidal history was replicated as the strongest predictor of future suicidal events in early psychosis (Hu et al., 1991; De Hert et al., 2001; Sinclair et al., 2004; Hawton et al., 2005; Reutfors et al., 2009; Dutta et al., 2010; Pompili et al., 2011; Björkenstam et al., 2014; Bakst et al., 2010a; Challis et al., 2013; Tarrier et al., 2006), including two recent meta-analyses (Large et al., 2011; Challis et al., 2013). However, it should be noted that up to 42% of patients with schizophrenia spectrum disorders who end their own lives have no suicidal history (Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016).

Sadly, most of the suicidal events over occurred a few days after a face-to-face appointment with a member of the staff, which is consistent with previous studies (Hu et al., 1991; Heilä et al., 1997; Tarrier et al., 2006; Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016), which appear to demonstrate the difficulties in predicting imminent suicide risk in the clinical setting.

The model tested in this research and the model based on the finding from this study are shown in figures 4.3 and 4.4, respectively, below.

Figure 4.3. Hypothesised model to be tested in this thesis.

Red arrows increase risk and green risk show reduced risk

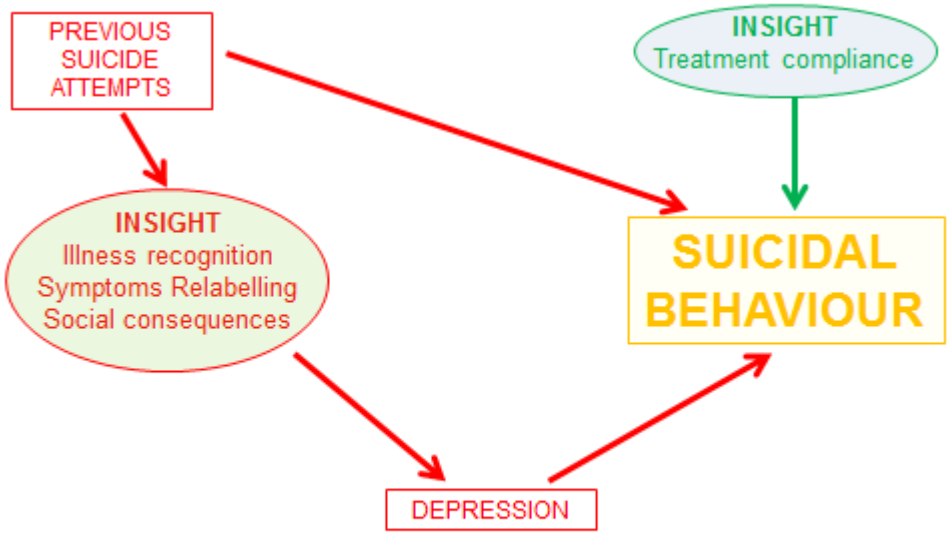
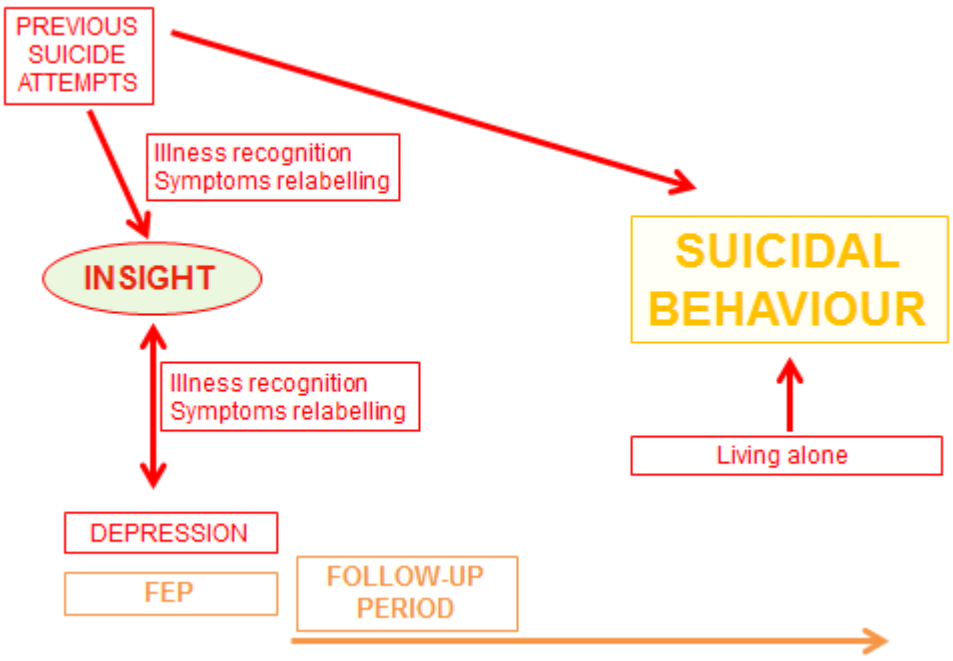


Figure 4.4. Model based on the GAP cohort study

Red arrows show higher risk



4.6.e. – Strengths and limitations

I recruited a representative sample of FEP, which was part of a large research project focused on the biological aetiology of psychosis, namely the Genetics and Psychosis Study (GAP). Thus, a number of variables were comprehensively evaluated by trained researchers. Also, participants were followed-up over a minimum period of 3 years, which has been reported to be the highest suicide risk period in psychosis (e.g. Palmer et al., 2005).

However, the study presented in this chapter has several limitations. Firstly, most of the negative results presented above should be interpreted with caution. For example, a potential type 2 error needs to be considered when interpreting these results since the statistical power for insight variables was 62.5%. As a result of this, I decided to merge this GAP sample with the AESOP cohort presented in chapter 5, which is detailed in chapter 6. Secondly, other non-tested variables might contribute to insight such as premorbid personality (Lysaker et al., 1999; Campos et al., 2011; Cuesta et al., 2011; Ritsner & Blumenkrantz, 2010) and neuroanatomical abnormalities (Morgan et al., 2010; David et al., 2012). Thirdly, examiners were not blind to other scales such as the PANSS, which might bias the insight assessment (Campos et al., 2011). Fourthly, our cross-sectional design did not allow me to capture the dynamics of insight (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011; Ayesa-Arriola & Lopez-Morinigo et al., 2014) since predictors of state-insight may change over the course of the illness and also, these time-related insight changes may affect suicide risk differently from insight levels at baseline. In keeping with this, demographic variables associated with suicide risk (for instance, living status) may have changed over the study follow-up, which was not recorded.

4.7. – Chapter summary

Although I found no relationships between insight dimensions and suicide risk in this FEP cohort over a 3-year follow-up, which was consistent with my hypotheses formulated in chapter 1, a type 2 error cannot be excluded. Accordingly, I decided i) to analyse a larger FEP cohort (Chapter 5); and ii) to merge both cohorts (chapter 6).

In addition, I will present the findings from a 3-year follow-up FEP study from Santander (Spain) in chapter 7, which I will compare with the above UK-based cohorts in the General Discussion (Chapter 8).

Chapter 5 – Suicidal behaviour in early psychosis. Findings from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study (UK)

5.1. – Introduction

This chapter describes the predictors of suicidal behaviour in a 10-year follow-up of a first-episode psychosis (FEP) cohort from the UK (London and Nottingham), which is part of the AESOP-10 study (Morgan et al., 2014; Reininghaus et al., 2014). In particular, I present the results of investigating the relationship of three insight dimensions, namely recognition of having a mental illness, symptom relabelling and awareness of the need for treatment, with suicidal acts over the follow-up, including suicide attempts (SA) and suicide completions (SC). I also adjusted these analyses for a set of demographic and clinical variables, which may mediate/confound the above relationships and therefore influence the rate of suicidal acts.

For the purposes of this thesis I have focused on suicidal events 'after' first presentation with psychosis, which is the main outcome measure, and I am thus considering survival to a first suicidal event over the follow-up period in relation to insight levels at baseline.

5.2. – Background

As detailed in chapter 2 and in chapter 4 (section 4.2), the role of insight dimensions in suicidal behaviour in FEP patients remains unclear (Lopez-Morinigo et al., 2012), and this may have important clinical implications for the development of suicide prevention measures focused on insight management from first presentation.

First, I will present the results from a replication study with an AESOP sample looking at the association of suicidal history prior to first presentation to services with multiple insight dimensions evaluated at that point. Second, I report the results from survival analyses aimed to examine the role of insight levels at first presentation in relation to time to a first suicidal act over the follow-up (median=10 years), whilst adjusting these analyses for a set of demographic and clinical variables which may mediate/confound the above relationships.

5.3. – Aims and Objectives

5.3.a. – Descriptive aims and objectives

- To describe the distribution of insight dimensions according to the outcome of suicidal behaviours, including both SA and SC.

5.3.b. – Analytical aims and objectives

- To investigate whether there is an association between a history of suicidal behaviours before first presentation with psychosis and insight levels at that point.
- To adjust the above analyses for a set of potential confounders in order to determine independent predictors of insight at baseline, including the role of previous suicidal history.
- To calculate the case fatality of this FEP sample over the 10-year follow-up.
- To identify the risk factors associated with suicidal behaviours in a FEP cohort over a 10-year follow-up.
    - And to determine whether there is an association of insight levels with risk of suicidal behaviours over the 10-year follow-up.
- To test for potential interactions between insight dimensions and other clinical and demographic variables related to risk of suicidal behaviour.
- To formulate a model, based on a multivariable Cox Regression analysis of the above baseline variables, including insight dimensions, for predicting suicidal behaviours over the 10-year follow-up.

5.4. – Method

5.4.a. – Recruitment and baseline assessment

The Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study is a multi-centre population based incidence and case-control study of first episode psychosis, conducted over a three-year period from September 1997 to August 2000. The primary aim of the AESOP study was to investigate the high rates of psychosis in African-Caribbean populations from the UK, and from this to shed light on the aetiology of psychosis in general. As the study progressed, the wealth of data collected and the measurement of outcomes at 10-year follow-up, including all-cause-mortality and suicide, allowed further questions to be addressed such as this thesis topic, namely the role of insight in suicide risk in early psychosis.

The inclusion criteria for cases were: a) age between 16 and 65 years; b) resident within tightly defined catchment areas in Nottingham or south-east London; and c) presence of a first episode of psychosis, namely F20-F29 and F30- F33 codes in ICD-10 within the time frame of the study.

Exclusion criteria were: a) evidence of psychotic symptoms precipitated by an organic cause; b) transient psychotic symptoms resulting from acute intoxication as defined by ICD-10; and c) IQ less than 50. Case finding procedures were based on those used by the World Health Organization (WHO) in its multi-country studies of the incidence and outcome of schizophrenia (Jablensky et al., 1992). A team of researchers was involved in regularly checking all points of potential patient contact with secondary and tertiary health services in the catchment areas.

Specifically, those potential cases who gave their written informed consent were screened for inclusion using the Screening Schedule for Psychosis (Jablensky et al., 1992), which was completed by interviewing the patient and/or using case notes and information provided by psychiatric staff. Each patient meeting inclusion criteria for the study was approached and informed consent sought. Case recruitment took place initially over two years in Nottingham and south-east London and nine months in Bristol. During the third year of the study, recruitment of African-Caribbean cases was extended in Nottingham and south-east London to increase the number of these patients in the case-control arm of the study. At the end of the period of case recruitment, a leakage study was conducted to identify further potential cases initially missed. For each patient included in the study, consent to interview a

close relative who had been in recent contact with the patient was also sought. Bristol participants were not followed-up and therefore, they were not included in this analysis.

Using the data obtained from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.0, WHO, 1992), which is an instrument designed to make psychiatric diagnoses (Janca et al., 1994), consensus diagnoses were established for each patient at regular AESOP Project meetings led by senior consultant psychiatrists. Those who did not meet the criteria for a functional psychotic disorder were excluded from the study. Patients in the AESOP study were asked to participate in a large number of assessments. One of those assessments was the Schedule for the Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997). The patients who took part in the SAI-E interview formed the subsample for this thesis. A summary of the AESOP study methods is provided in box 4.1, some of which were used for this thesis.

Box 5.1. – AESOP study

Biological: Magnetic resonance imaging, DNA.

Clinical: Schedules for Clinical Assessment in Neuropsychiatry, Personal and Psychiatric History Schedule, Schedule for Assessment of Insight – Expanded version.

Psychosocial: MRC Sociodemographic Schedule, Culture and Identity Schedule, Achievements and Expectations Schedule, Employment Schedule, Significant Others Schedule, Childhood Experiences of Care and Abuse Questionnaire, Life Events and Difficulties Schedule, Mental Disorder Beliefs Schedule, Locus of Control, Self-Esteem, Self-Concept.

Cognitive: neuropsychological test battery, Neurological Soft Signs, Minor Physical Abnormalities, Family Interview for Genetics.

5.4.b. – Follow-up: the AESOP-10 study

In order to collect as much information as practicable at 10 years after the study inception, a comprehensive tracing procedure was carried out by AESOP researchers (for further methodological details, see Morgan et al., 2014).

Briefly, those patients who were in contact with mental health services at approximately 10 years were contacted via the clinical teams and invited to participate in the study. For those who were not under mental healthcare, up to two letters were sent to their last known address inviting them to participate. In addition, researchers made a maximum of three visits to the address (morning, afternoon and evening on different days) to make initial contact. For those who had moved address, and for whom GP details were available, an invitation letter was sent to the GP.

Either from face-to-face interviews or from clinical records, the World Health Organization (WHO) Life Chart (Sartorius et al., 1996) was used to collate extensive information on three domains – clinical (including suicide attempts), social and mental health service use.

In addition, with regard to mortality data, including suicide, a person-tracing procedure was conducted on behalf of the AESOP team by the Office for National Statistics (ONS) using name, sex, date of birth and last known address. For all identified deaths, ICD-10 codes of the official cause of death (according to the ONS certificate of death) were recorded (see Reininghaus et al., 2014 for further details).

5.4.c. – Measures

5.4.c.1. – Premorbid, sociodemographic and clinical variables

Information was obtained from patients, relatives and medical records. This included sex, age at admission, age at onset, ethnicity and duration of untreated psychosis (DUP). Specifically, the time from the date of the first psychotic symptom to the date of first contact with services was taken.

Other sociodemographic variables collected were: level of education, relationship status ("married" vs. "unmarried"), living status ("alone" vs. "other"), employment status ("employed" vs. "unemployed"), cannabis ('use' and 'abuse/dependence' were both dichotomized as present/absent, respectively) and alcohol ('use' and 'abuse/dependence' were both dichotomized as present/absent, respectively).

5.4.c.2. – Neurocognitive tests

The National Adult Reading Test (NART) (Nelson & Willison, 1991) was used to evaluate the premorbid Intelligence Quotient (IQ). Also, the short version of the Wechsler Adult Intelligence Scale Revised (WAIS-R, Wechsler, 1981) provided an accurate estimate of the current IQ (full scale).

Executive functions were assessed by the Trail Making Test (Reitan, 1958), which involves connecting numbers (Trails A) or alternating numbers and letters (Trails B). The time (in seconds) taken to complete the task was the dependent variable. Subtracting time to complete Trails A from Trails B gives an overall measure of executive function, after having controlled for the effect of processing speed.

5.4.c.3. – Psychopathological symptoms

Symptom data in AESOP were collected using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO, 1992). The SCAN incorporates the Present State Examination Version 10, which was used to elicit symptom-related data at the time of presentation. All SCAN interviews were conducted as soon as possible after first contact with psychiatric services. For the purposes of the analysis, symptom ratings were calculated according to the SCAN's Item Group Checklist (IGC) algorithm. The IGC is advantageous in reducing the

number of symptoms and signs entering the analysis and also allows for a case-notes and informant-based (e.g. health professionals, close relatives) assessment of symptoms to be carried out when it is not possible to conduct a face-to-face patient interview. The IGC combines scores on 31 SCAN items specific to particular groups of symptoms. For instance, an IGC item, 'special features of depressed mood', includes loss of feeling, unremitting depression, morning depression, preoccupation with catastrophe, pathological guilt, guilty ideas of reference, loss of self-esteem and dulled perception. Scores for individual item groups range from 0 (absent) to 2 depending on the frequency and severity of symptoms. The choice of items to be included in the analysis was guided by previous studies that had used the PSE (Liddle, 1987; Mellers et al. 1996, Hutchinson et al. 1999). A factor analysis with an overlapping AESOP sample (Demjaha et al., 2009) yielded five psychopathological dimensions: reality distortion (or positive), negative, disorganization, mania and depression.

5.4.c.4. – Insight

The Schedule for Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997) was used to evaluate insight (see section 4.4.b.2 for further details).

5.4.c.5. – Suicide attempts information

Suicidal behaviours were taken from medical records and defined as 'any potentially self-injurious behaviour for which the person intended to kill himself/herself' (O'Carroll et al., 1996), which included SA and SC both before and after first presentation to services. Those subjects with information on suicidal behaviour available, including censoring dates, were included.

In addition, I identified all occurrences of death and emigration in the cohort over the follow-up via a person-tracing procedure conducted on my behalf by the Office for National Statistics (ONS) for England and Wales and the General Register Office (GRO) for Scotland using name, sex, date of birth, and last known address. For all identified deaths, principal underlying causes of death were determined according to the International Classification of Diseases, 10th revision (ICD-10), as recorded on copies of death certificates obtained from ONS. I classified as 'suicides' those subjects with the following ICD-10 codes of death according to the ONS: X60–X84 and Y10–Y34.

5.4.d. – Statistical analysis

The Statistical Package for Social Science version 22.0 (SPSS Inc., Chicago, IL, USA) was used for performing the statistical analyses. Descriptive analyses and comparison of patient characteristics, including the aforementioned demographic and clinical variables, were undertaken using chi-square, t-tests and Mann-Whitney U tests as appropriate.

First, predictors of insight dimensions at baseline were investigated through binary logistic regression models in order to precisely test the influence of suicidal history on insight levels after adjusting the analyses for potential mediating variables.

Second, all patients were entered into a survival analysis with the end date being the date of first suicide attempt (or suicide completion where appropriate) or the censoring point, i.e. either the date on which the patient was last known to be alive or the end of the follow-up study period, which commenced at the time of discharge from hospital or after first contact to services in those patients who were not admitted at first presentation.

Case-fatality (Palmer et al., 2005) was estimated based on the number of suicides identified at the end of the follow-up (numerator) and the initial sample size (denominator).

Survival analyses (Kaplan-Meier Curves and log-rank tests) were performed to compare time from hospital discharge, or first appointment for those outpatients who did not require hospitalization, to first suicidal event or the censoring point as appropriate with insight levels at baseline. Participants were censored as non-attempters at the time of the last face-to-face assessment with a member of staff.

In addition, multivariable Mandel-Cox regression models (Cox, 1972) investigated time to first suicidal event in relation to baseline insight variables, whilst adjusting the analyses for potential mediating/confounding demographic and clinical variables.

All of the above analyses were two-tailed and significance level was set at 5%.

5.4.d.1. – Power calculations

As explained in chapter 4 (section 4.4.c.1) I used the *stpower logrank* command of STATA 11.0 for Windows (StataCorp LP, USA) to conduct the power calculations based on the number of patients with information on insight and suicidal behaviour available.

In particular, the FEP cohort presented in this chapter was followed-up over 10 years (median). Based on previous FEP studies, it is expected that at the end of the follow-up at least 20% of the initial sample size will have made one suicide attempt (e.g. Robinson et al., 2010), including 2-5% of suicides (Dutta et al., 2010; Palmer et al., 2005). Given that the mean SAI-E score for FEP patients is around 13/28 with a standard deviation of around 6 (e.g. Morgan et al., 2010), a difference of 2 points (e.g. 13 vs 15) between suicide attempters and non-attempters, which is considered to be clinically meaningful (Kemp & David, 1997), is equivalent to an effect size of 0.33 with a two-tailed alpha set at 5%. Under these assumptions I will have 75.1% power to detect such 2-point difference in this sample (n=157).

5.5. – Results

5.5.a. – Baseline demographic and clinical characteristics of the sample

The sample was comprised of N=181 FEP cases from the AESOP study. The sociodemographic and clinical characteristics of the whole sample, including the number of patients with information available on each variable, and differences between those with/without SA prior to first presentation are presented in Table 5.1. below.

Table 5.1. AESOP: Demographic and clinical differences between patients with/without previous suicide attempts

	Data availability N (%)	Total sample	With previous SA n = 16 (9.9%)	Without previous SA n = 146 (90.1%)	Statistic	p-value
Age at first contact, years	181 (100)	30.5 ± 11.3	31.4 ± 11.5	31.4 ± 11.2	t=-0.0	0.97
Gender, males	181 (100)	101 (55.8)	8 (50.0)	78 (53.4)	X^2=0.1	0.79
Level of education	**162 (89.5)**					
No qualifications		**51 (31.5)**	**9 (56.2)**	**42 (28.8)**	**X^2=5.0**	**0.02**
≥GCSE		**111 (68.5)**	**7 (43.7)**	**104 (71.2)**		
Unmarried	162 (89.5)	111 (67.7)	9 (56.2)	99 (67.8)	X^2=0.8	0.35
Living alone	168 (92.8)	52 (31.0)	5 (39.0)	45 (28.9)	X^2=0.4	0.53
Unemployed	175 (96.7)	78 (44.6)	8 (50.0)	61 (41.8)		
Ethnicity	181 (100)				X^2=0.2	0.63
White		101 (55.8)	10 (62.5)	82 (56.2)	X^2=1.4	0.23
Black		61 (33.7)	3 (18.7)	49 (33.6)	X^2=1.0	0.30
Other		19 (10.5)	3 (18.7)	15 (10.3)	U	0.06
DUP: days, median	166 (91.7)	49.5	51	47		
Diagnosis (ICD-10)	181 (100)				X^2=0.0	0.92
Schizophrenia spectrum		**118 (65.2)**	**10 (62.5)**	**93 (63.7)**	**X^2=4.0**	**0.04**
Mania with psychosis		**31 (17.1)**	**0 (0)**	**30 (20.5)**	**X^2=4.6**	**0.03**
Psychotic depression		32 (17.7)	6 (37.5)	23 (15.7)		
Drugs use	175 (96.7)				X^2=0.8	0.38
Use		103 (58.9)	7 (46.7)	83 (58.4)		
Alcohol	180 (99.4)				X^2=0.0	0.83
Use		152 (84.4)	14 (87.5)	124 (85.5)		

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
SA: Suicide attempts (before first contact).
GCSE: General Certificate of Secondary Education

5.5.b. – Insight

5.5.b.1. – Values and scores distribution

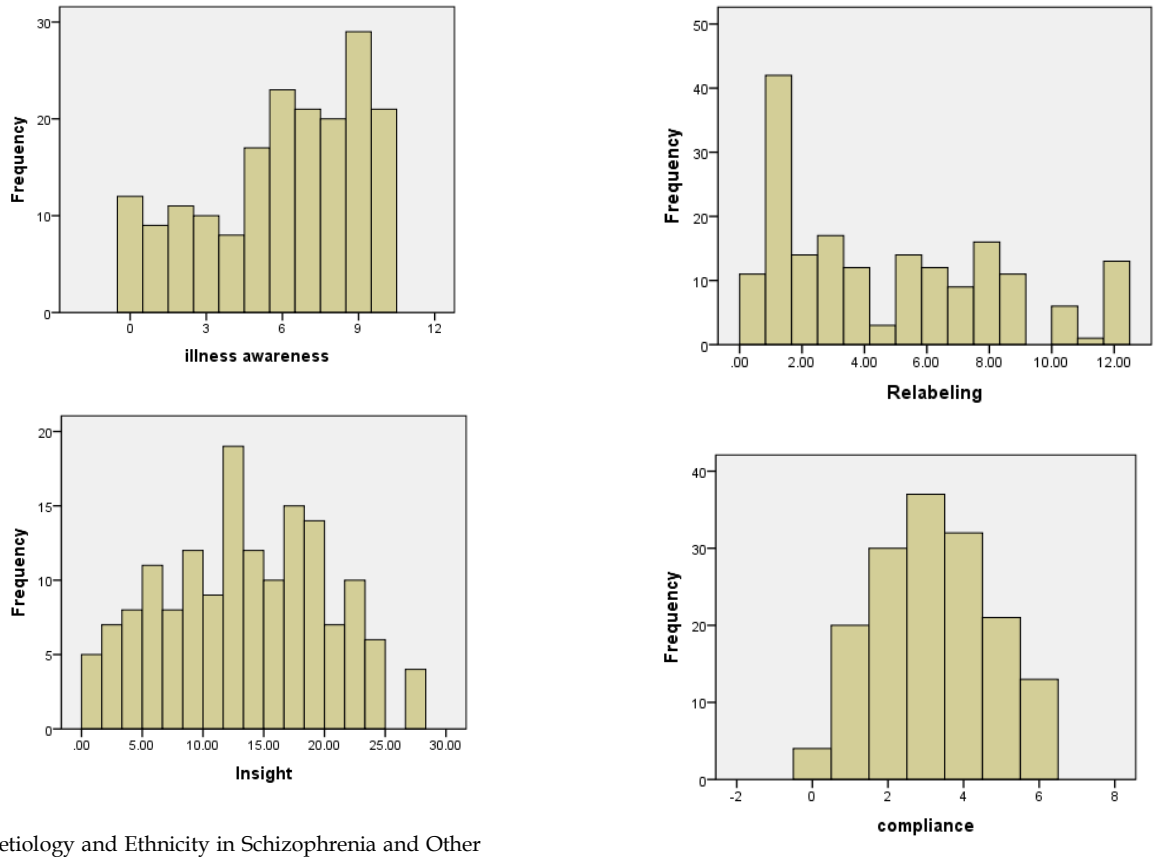
The insight total scores and insight dimensions levels are summarised in table 5.2. In particular, the mean, standard deviation (SD), median and range of scores for recognition of illness, symptoms relabelling, treatment compliance and the total insight are presented. Kolmogorov-Smirnov tests confirmed normal distribution for total insight scores, while insight dimensions were not normally distributed.

Table 5.2. Insight levels across the AESOP sample (N=181)

	n (%)	Mean ± SD	Median	Min - Max	K-S test
Recognition	**181 (100)**	**6.0 ± 3.0**	**7.0**	**0 – 10**	**<0.01**
Relabelling	**181 (100)**	**4.7 ± 3.6**	**4.0**	**0 – 12**	**<0.01**
Compliance	**157 (86.7)**	**3.2 ± 1.5**	**3.0**	**0 – 6**	**0.01**
Total insight	157 (86.7)	13.6 ± 6.6	13.3	0 - 28	0.69

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
SD: Standard Deviation.
K-S: Kolmogorov-Smirnov Test

Figure 5.1. AESOP. Distribution of insight scores



AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses

5.5.b.2. - Correlations between insight dimensions

All insight dimensions showed significant ($p<0.01$) and positive correlations between themselves. Specifically, symptom relabelling and treatment compliance showed the weakest correlation ($r=0.36$), while relabelling and recognition had the strongest correlation ($r=0.54$). All these correlations are presented in table 5.3. below.

Table 5.3. AESOP. Correlation matrix* of theoretical insight dimensions (n=157-181)

	Recognition	Relabelling	Compliance
Recognition		0.54	0.53
Relabelling	0.54		0.36
Compliance	0.53	0.36	

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
*Spearman r coefficients, all significant at $p<0.01$(two-tailed)

5.5.b.3. – Factor analysis

As conducted in chapter 4 (section 4.5.b.3.), an exploratory factor analysis with Varimax rotation was performed in order to assess the degree of similarity between these data and the 3-factor model proposed by David (David, 1990). In this sample, a 3-factor solution was replicated (eigenvalues over 1), which explained 40.6%, 13.0% and 9.4% of the variance, respectively; hence 63.4% of the variance on total insight.

However, in this 3-factor solution item 9 of the SAI-E (hypothetical contradiction) emerged significant within the 'symptoms relabelling' factor (i.e. factor 2) and item 6 (awareness of the need for treatment) was captured by 'illness recognition' rather than 'treatment compliance'. See table 5.4 below.

Table 5.4. AESOP. Factor loadings following a Varimax rotation on the SAI-E

Principal Component Matrix*				
		Factors		
SAI-E item	**Insight dimensions**	**1**	**2**	**3**
1	Recognition	0.75	0.16	0.01
2		0.68	0.30	0.13
3		0.67	0.38	0.05
4		0.60	0.53	0.04
5		0.59	-0.16	0.30
6		0.69	0.18	0.17
7	Relabeling	0.19	0.87	0.09
8		0.24	0.85	0.15
9		0.14	0.81	0.04
10	Compliance	0.20	-0.01	0.75
11		0.25	0.25	0.76
Initial eigenvalues		**4.47**	**1.43**	**1.03**
Variance explained (%)		**40.6**	**13.0**	**9.4**

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.
*Rotation converged in 6 iterations.
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SAI-E: Schedule for Assessment of Insight – expanded version (Kemp & David, 1997)

5.5.c. – Differences between patients with/without suicidal history in insight levels, psychopathology and neurocognitive variables

I replicated the associations of illness awareness and total insight with suicidal history as detailed in table 5.5. below. However, neither symptom relabeling nor treatment compliance showed such relationships.

In addition, the severity of one psychopathological domain, namely depression, significantly differed across groups.

No significant differences in neurocognitive variables emerged from the analyses.

Table 5.5. AESOP: Differences in insight, psychopathology and neurocognitive variables between patients with/without previous suicide attempts

	Data availability N (%)	Total sample	With previous SA	Without previous SA	Statistic	p-value
Insight scores						
Recognition	**181 (100)**		**n=16**	**n=146**		
		6.0 ± 3.0	**7.6 ± 1.9**	**5.9 ± 3.0**	**t=3.1**	**<0.01**
Relabelling	181 (100)		n=16	n=146		
		4.7 ± 3.6	5.5 ± 3.3	4.7 ± 3.7	t=0.82	0.41
Compliance	**157 (86.7)**		**n=15**	**n=127**		
		3.2 ± 1.5	**4.0 ± 1.4**	**3.2 ± 1.5**	**t=1.9**	**0.05**
Total Insight	**157 (86.7)**		**n=15**	**n=127**		
		13.6 ± 6.6	**17.2 ± 5.0**	**13.4 ± 6.7**	**t=2.1**	**0.03**
Psychopathology	156 (86.2)		n=16	n=133		
Positive		4.0	4.5	4.0	U	0.26
Negative		1.0	2.0	0.0	U	0.05
Disorganization		0.0	0.0	0.0	U	0.51
Mania		1.0	0.0	1.0	U	0.07
Depression		**0.0**	**5.0**	**0.0**	**U**	**<0.01**
Premorbid IQ	*133 (73.4)*		*n=35*	*n=127*		
Verbal		96.6 ± 13.5	96.8 ± 15.9	97.6 ± 13.0	t=-0.2	0.82
Performance		98.1 ± 13.0	98.3 ± 15.6	99.1 ± 12.6	t=-0.2	0.83
Full		97.2 ± 14.6	97.6 ± 17.5	98.3 ± 14.2	t=-0.2	0.86
Current IQ	*147 (81.2)*		*n=12*	*n=119*		
		89.6 ± 16.0	89.0 ± 16.0	91.0 ± 16.5	t=-0.4	0.69
TMT-A (seconds)	*145 (80.1)*		*n=11*	*n=119*		
		47.2 ± 27.0	50.0 ± 24.0	45.1 ± 24.8	t=0.6	0.53
TMT-B (seconds)	*140 (77.3)*		*n=11*	*n=114*		
		107.3 ± 62.5	127.2 ± 77.3	102.7 ± 60.3	t=1.2	0.21
TMT-B-A (seconds)	*138 (76.2)*		*n=11*	*n=112*		
		60.9 ± 46.4	77.2 ± 68.9	58.6 ± 45.4	t=0.9	0.40

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

5.5.d. – Bivariate analyses: relationships between insight dimensions and baseline demographic and clinical characteristics of the sample

Exploratory analyses investigated potential relationships between insight levels (as dependent variable) and a wide range of baseline demographic variables. In particular, no significant differences in insight scores emerged from between-group comparisons with regard to age at first contact.

However, symptom relabelling and total insight were significantly greater in females than in males.

Also, those with 'qualifications' (i.e. GCSE levels or higher education) showed significantly higher levels of symptom relabelling than those without qualifications. Insight levels did not vary in terms of marital, living and employment status.

However, patients of White ethnicity were found to have greater levels of illness recognition and total insight than Black patients.

See table 5.6. below for further details.

Table 5.6. AESOP: Baseline demographic data and insight levels

	Recognition	Relabelling	Compliance	Total insight
Age at first contact	*n=164*	*n=164*	*n=144*	*n=144*
	r=-0.07	r=-0.14	r=0.04	r=-0.08
	p=0.36	r=0.07	p=0.62	p=0.32
Gender	*n=181*	***n=181***	*n=157*	***n=157***
Males	5.7 ± 3.1	**4.1 ± 3.1**	3.1 ± 1.6	**12.6 ± 6.4**
Females	6.4 ± 3.0	**5.4 ± 3.9**	3.3 ± 1.4	**14.9 ± 6.8**
	t=-1.5, p=0.15	**t=-2.4, p=0.02**	t=-1.1, p=0.28	**t=-2.1, p=0.04**
Level of education	*n=175*	***n=175***	*n=153*	*n=153*
No qualifications	5.7 ± 3.3	**3.8 ± 3.5**	3.1 ± 1.6	12.5 ± 7.0
≥ GCSE	6.3 ± 2.9	**5.1 ± 3.5**	3.3 ± 1.5	14.5 ± 6.4
	t=-1.1, p=0.29	**t=-2.3, p=0.02**	t=-0.9, p=0.38	t=-1.7, p=0.08
Marital status	*n=169*	*n=169*	*n=148*	*n=148*
Unmarried	5.8 ± 3.0	4.8 ± 3.7	3.1 ± 1.6	13.4 ± 7.1
Married	6.5 ± 3.0	4.6 ± 3.3	3.5 ± 1.3	14.4 ± 5.8
	t=-1.4, p=0.15	t=-0.2, p=0.81	t=-1.7, p=0.09	t=-0.9, p=0.38
Living status	*n=168*	*n=168*	*n=147*	*n=147*
Alone	5.9 ± 3.1	4.5 ± 3.6	3.2 ± 1.5	13.7 ± 7.0
With others	6.1 ± 2.9	4.8 ± 3.6	3.3 ± 1.6	13.7 ± 6.5
	t=-0.4, p=0.72	t=-0.5, p=0.63	t=-0.2, p=0.84	t=-0.0, p=0.99
Employment status	*n=175*	*n=175*	*n=153*	*n=153*
Unemployed	5.7 ± 3.3	4.3 ± 3.6	3.0 ± 1.7	12.7 ± 7.2
Employed	6.4 ± 2.7	5.1 ± 3.5	3.4 ± 1.4	14.7 ± 5.9
	t=-1.6, p=0.10	t=-1.5, p=0.14	t=-1.4, p=0.16	t=-1.8, p=0.06
Ethnicity	***n=181***	*n=181*	*n=157*	***n=157***
White	**6.6 ± 2.9**	5.5 ± 3.5	3.4 ± 1.4	**14.8 ± 6.2**
Black	**5.2 ± 3.3**	4.0 ± 3.6	2.8 ± 1.6	**11.7 ± 6.9**
Others	**5.5 ± 2.5**	4.9 ± 3.3	3.1 ± 1.7	**13.8 ± 7.0**
	F=4.8, p<0.01	F=1.8, p=0.16	F=2.5, p=0.08	**F=3.7, p=0.03**

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
GCSE: General certificate of Secondary Education

With regard to baseline clinical characteristics of the sample such as DUP, diagnosis and alcohol and illicit drugs use, no significant differences emerged from the bivariate analyses which are shown in table 5.7. below.

Table 5.7. AESOP: Baseline clinical characteristics and insight dimensions

	Recognition	**Relabelling**	**Compliance**	**Total Insight**
DUP	*n=166*	*n=166*	*n=146*	*n=146*
<49.5 days	6.4 ± 2.9	5.1 ± 3.7	3.5 ± 1.5	14.5 ± 6.9
>49.5 days	5.8 ± 3.0	4.3 ± 3.4	3.1 ± 1.6	13.1 ± 6.4
	t=1.2, p=0.23	t=1.4, p=0.15	t=1.5, p=0.13	t=1.3, p=0.20
Diagnosis	*n=181*	*n=181*	*n=157*	*n=157*
Schizophrenia	5.8 ± 3.1	4.5 ± 3.7	3.2 ± 1.6	13.3 ± 7.0
Mania	5.7 ± 3.2	5.3 ± 3.4	2.6 ± 1.3	12.9 ± 6.4
Depression	7.2 ± 2.4	4.8 ± 3.1	3.5 ± 1.3	15.2 ± 5.1
	F=2.8, p=0.06	F=0.6, p=0.54	F=2.6, p=0.07	F=0.9, p=0.38
Alcohol	*n=180*	*n=180*	*n=156*	*n=156*
Use	6.1 ± 2.9	4.9 ± 3.6	3.2 ± 1.6	13.8 ± 6.6
non-use	5.8 ± 3.5	3.6 ± 3.3	3.1 ± 1.5	12.5 ± 6.7
	t=-0.4, p=0.65	t=-1.7, p=0.08	t=-0.2, p=0.87	t=-0.9, p=0.36
Drugs	*n=175*	*n=175*	*n=151*	*n=151*
Use	6.2 ± 3.1	4.8 ± 3.6	3.2 ± 1.7	13.8 ± 6.9
non-use	5.9 ± 2.9	4.6 ± 3.7	3.2 ± 1.4	13.4 ± 6.4
	t=-0.6, p=0.57	t=-0.3, p=0.79	t=-0.2, p=0.82	t=-0.4, p=0.71

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
DUP: Duration of untreated psychosis

I also conducted correlation analyses between insight scores and psychopathological dimensions and neurocognitive variables, which are detailed in table 5.8. below, which revealed several significant differences. In terms of significant associations of psychopathological domains and insight dimensions, depression correlated positively with all insight scores, while compliance showed a negative relationship with disorganization and mania. In addition, the positive dimension showed an inverse association with symptoms relabeling.

Regarding neurocognitive variables, the directions of the associations was that the worse the cognitive performance, the poorer the insight. Specifically, current IQ and TMT-A and TMT-B correlated with illness recognition and relabeling, which also correlated with premorbid IQ (including verbal, performance and full IQ). Total insight showed a relationship with current IQ and TMT-A.

Table 5.8. AESOP: Correlations of insight dimensions with psychopathological and neurocognitive variables

	Recognition			Relabelling			Compliance			Total Insight		
	n	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**
Positive	156	-0.05	0.52	**156**	**-0.20**	**0.02**	137	0.03	0.70	137	-0.12	0.17
Negative	156	-0.08	0.34	156	-0.02	0.80	137	0.04	0.61	137	-0.06	0.51
Disorganization	156	0.00	0.94	156	-0.03	0.65	**137**	**-0.20**	**0.02**	137	-0.03	0.72
Mania	156	-0.06	0.46	156	-0.09	0.94	**137**	**-0.18**	**0.03**	137	-0.09	0.30
Depression	**156**	**0.23**	**<0.01**	**156**	**0.18**	**0.04**	**137**	**0.26**	**<0.01**	**137**	**0.18**	**0.04**
Premorbid IQ	199	0.05	0.30	**199**	**0.21**	**0.01**	172	0.04	0.62	172	0.13	0.13
IQ (WAIS-III)	**202**	**0.22**	**0.01**	**202**	**0.23**	**0.01**	174	0.12	0.20	**174**	**0.27**	**<0.01**
TMT-A (seconds)	**195**	**-0.24**	**<0.01**	**195**	**-0.19**	**0.02**	170	-0.09	0.28	**170**	**-0.29**	**<0.01**
TMT-B (seconds)	**190**	**-0.21**	**0.01**	**190**	**-0.18**	**0.03**	165	-0.06	0.49	165	-0.15	0.11
TMT B-A (seconds)	187	-0.16	0.05	187	-0.16	0.07	163	0.04	0.64	163	-0.03	0.78

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
IQ: Intelligence Quotient. WAIS: Wechsler Adult Intelligence Scale, revised (Wechsler, 1981). TMT: Trail Making Test (Reitan, 1958).

5.5.e. – Regression on recognition of illness

A hierarchical linear regression model ('enter' method) was performed to reassess the association of previous SA with recognition of illness whilst adjusting for some variables which had also been associated with illness recognition, namely being white, neurocognition (current IQ and TMT-A) and depressive symptoms severity. Of note, the block of variables that remained significant was neurocognition. The final model accounted for 11% of the variance on recognition.

Table 5.9. AESOP: Regression on recognition

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				*0.029*	*0.06*
White	0.42	0.56	0.46		
Block 2:				*0.014*	*0.20*
Previous SA	0.84	0.96	0.38		
Block 3:				*0.052*	*0.04*
Current IQ	0.02	0.02	0.22		
TMT-A	-0.02	0.01	0.14		
Block 4:				*0.015*	*0.18*
Depression	0.21	0.15	0.18		
GLOBAL R^2				0.11	

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SA: suicide attempts prior to first presentation
IQ: Intelligence Quotient. TMT-A: Trail Making Test (task A) (Reitan, 1958)

5.5.f. – Regression on relabelling of symptoms

A hierarchical linear regression model ('enter' method) was carried out to reassess the association of previous SA with symptoms relabelling after controlling for the effects of education level (no qualifications vs. higher level), gender (male vs. female), neurocognition (premorbid and current IQ and TMT-A to avoid multi-collinearity) and positive and depressive symptoms severity. Gender (p=0.04) was the only variable that remained significant in the final model, which explained 14% of the variance on relabelling of symptoms.

Table 5.10. AESOP: Regression on relabelling

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				*0.061*	*0.03*
Gender (male)	-1.40	0.67	0.04		
No qualifications	-0.83	0.80	0.30		
Block 2:				*0.054*	*0.08*
Premorbid IQ	0.00	0.03	0.84		
Current IQ	0.03	0.03	0.33		
TMT-A	-0.02	0.01	0.13		
Block 3:				*0.027*	*0.18*
Positive	-0.17	0.12	0.17		
Depression					
GLOBAL R^2				0.14	

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
IQ: Intelligence Quotient. TMT-A: Trail Making Test, task A (Reitan, 1958)

5.5.g. – Regression on treatment compliance

Only three psychopathological dimensions, namely disorganization (negative association), mania (negative association) and depression (positive relationship) were related to compliance, none of which survived the multivariable regression model.

Table 5.11. AESOP: Regression on compliance

	B	SE	R^2 Change	p-change
Disorganization	-0.02	0.13	0.00	0.95
Mania	-0.09	0.05	0.02	0.60
Depression	-0.04	0.16	0.00	0.86

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses

5.5.h. – Regression on total insight

A hierarchical linear regression model ('enter' method) was carried out to reassess the association of suicidal history with total insight after controlling for the effects of demographic variables, such as education level (no qualifications vs. higher education), gender (male) and being white, neurocognitive variables (current IQ and TMT-A) and depressive symptoms severity. Gender remained significant, while depression showed a borderline association with total insight. The model accounted for 14% of the variance on total insight, which is detailed in table 5.12. below.

Table 5.12. AESOP: Regression on total insight

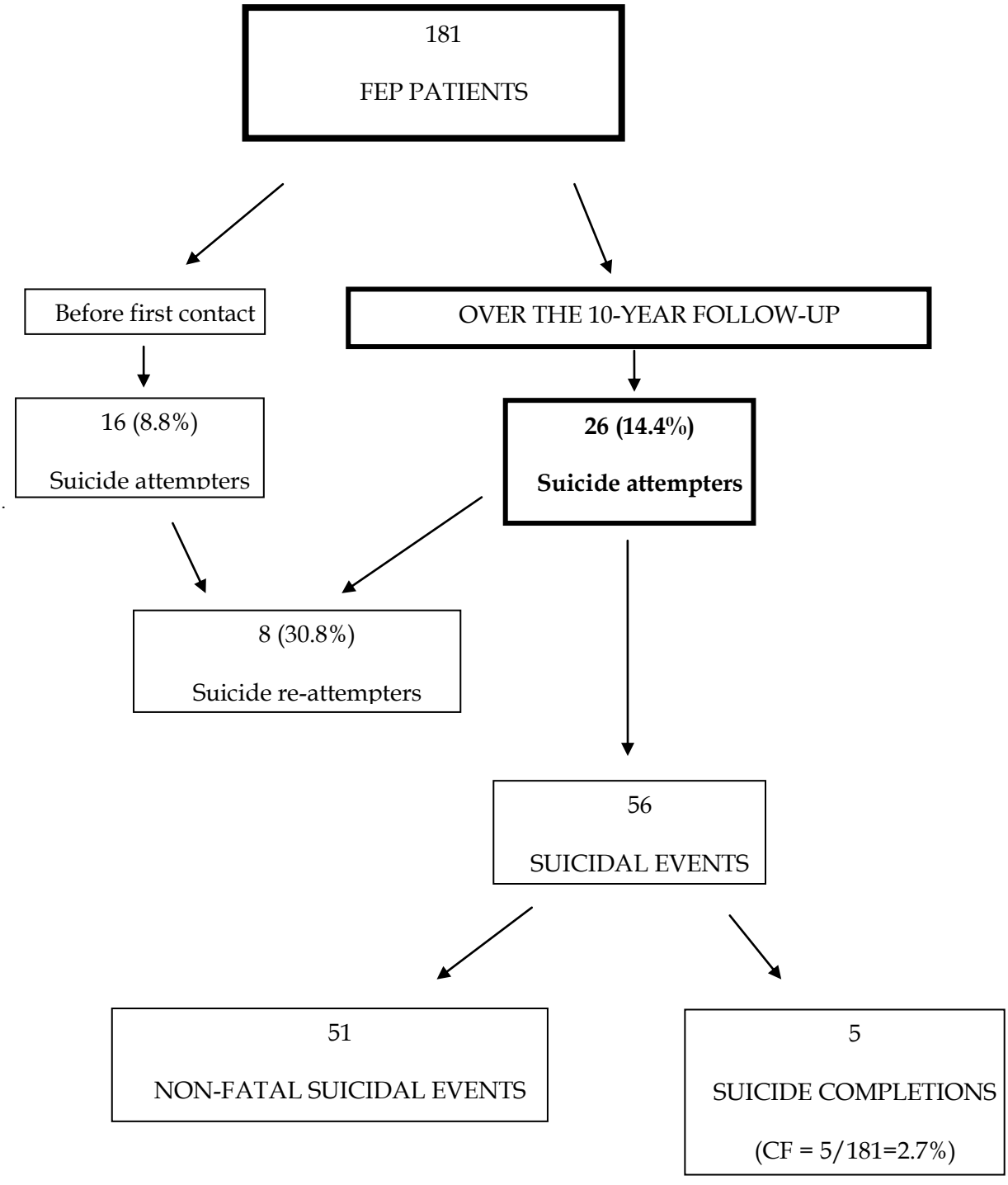
	B	SE	p	R^2 Change	p-change
Block 1:				*0.072*	*0.04*
Gender (male)	-1.51	0.68	0.03		
No qualifications	-1.16	0.81	0.15		
White	0.13	0.74	0.86		
Block 2:				*0.005*	*0.42*
Previous SA	1.65	1.25	0.19		
Block 3:				*0.037*	*0.10*
Current IQ	0.03	0.03	0.25		
TMT-A	-0.02	0.02	0.26		
Block 4:				*0.023*	*0.09*
Depression	-0.34	0.20	0.09		
GLOBAL R^2				0.14	

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SA: suicide attempts prior to first presentation
IQ: Intelligence Quotient. TMT-A: Trail Making Test (task A) (Reitan, 1958)

5.5.i. – Suicidal behaviours over the 10-year follow-up

In total, 34 subjects (18.7%) made at least one suicide attempt either prior to first contact with services or over the follow-up, which had a median of 10 years. Specifically, 26 individuals (14.4%) attempted to take their lives over the follow-up, 8 of whom (4.4%) were re-attempters, i.e. they made suicidal acts before and after first contact. In total, 16 subjects had attempted to take their lives before first presentation. Eight patients made two suicide attempts over the follow-up, three individuals attempted to end their lives on three occasions and four patients made multiple suicide attempts (from 4 to 7). Five subjects died from suicide over the 10-year that period, which yielded a case fatality of 5/181=2.7%. In addition, 6 more patients died from natural causes within the 10-year follow-up. Regarding attrition, 10 patients (5.5%) could not be traced or they were abroad at 10-year follow-up. See figure 5.2. below.

Figure 5.2. Flow chart of AESOP patients

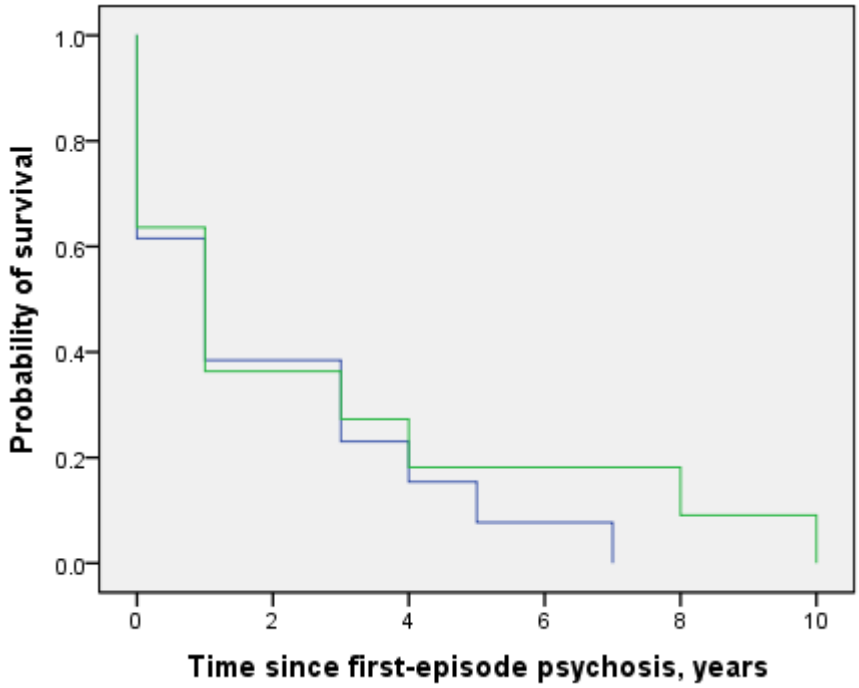


AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
FEP: First-episode psychosis
CF: Case-fatality

Thus, 26 suicide attempters, including the 5 individuals who ended their lives, and 155 non-suicide attempters were compared through Kaplan-Meier survival analyses and Cox Regression models with regard to baseline insight levels, whilst adjusting the analyses for a set of demographic and clinical variables.

Of note, the median of time to first suicide attempt was one year with non-significant (p=0.47) differences across genders (males in green and females in blue), as shown by the Kaplan-Meier Curve below which also (Figure 5.3.).

Figure 5.3. AESOP. Kaplan-Meier Curve for those who attempted and/or completed suicide (n=26) over the 10-year follow-up



AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses

5.5.i.1. – Suicide methods

As detailed in figure 5.2 above, there were 56 suicidal events over the follow-up. Thus, poisoning (n=16) and jumping (n=9), which included both jumping off a high place and jumping in front of a vehicle, were the most common suicide methods. Also, there were suicide attempts by violent methods such as stabbing (n=1) or arson (n=1). There were no suicide attempts by firearms.

Also, 5 subjects ended their lives, who were all males. In particular, two subjects hanged themselves, one patient jumped in front of a train, another individual stabbed himself to death and 'other' method was used by the remaining suicide completer.

Table 5.13. AESOP. Suicide methods

Method	Events (n=56)
Poisoning	16
Cutting superficially	6
Stabbing*	1
Jumping*	9
Hanging*	5
Setting a fire	1
Drowning	1
Unspecified*	1
Unrecorded	16

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
*at least one suicide completion by this mean

5.5.j. – Risk factors for suicidal behaviour over the follow-up

Univariate analyses concerning demographic, clinical and symptom-related variables, including insight, are presented below in tables 5.14, 5.15 and 5.16, respectively.

Table 5.14. AESOP: Univariate analysis: log-rank tests of equality of survival distributions for the demographic variables (n=166)

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Gender	Male	12.8	11	0.75	0.39
	Female	11.1	13		
Age at first contact	<28	11.7	12	0.00	0.95
	>28	12.3	12		
Education level	No qualifications	2.8	2	0.22	0.64
	≥ GCSE	6.2	7		
Marital status	Unmarried	6.0	5	0.67	0.41
	Married	2.3	4		
Living status	Alone	7.6	10	1.25	0.26
	Not alone	16.4	14		
Employment status	Unemployed	10.4	8	1.01	0.32
	Employed	13.6	16		
Ethnicity	White	13.4	16	1.84	0.40
	Black	7.9	5		
	Other	2.6	3		

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
GCSE: General Certificate of Secondary Education

Table 5.15. AESOP: Univariate analysis: log-rank tests of equality of survival distributions for the clinical variables (n=166)

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Previous SA	**Absent**	**21.6**	**16**	**23.11**	**<0.01**
	Present	**2.4**	**8**		
DUP	<49.5	12.0	11	0.22	0.64
	>49.5	12.0	13		
Diagnosis	Schizophrenia	15.2	16	0.76	0.68
	Mania	4.5	3		
	Depression	4.3	5		
Drugs	non-use	10.4	9	0.38	0.54
	Use	13.6	15		
Alcohol	**non-use**	**3.6**	**0**	**4.49**	**0.03**
	Use	**20.4**	**24**		

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SA: suicide attempts prior to first presentation

As shown in tables 5.14, 5.15., above, and 5.16 and 5.17., below, only three variables emerged as significant factors associated with time to first suicidal event, namely suicidal history (RR 2.92, 95% CI 0.96-8.86, p=0.06), an overall measure of executive functions such as TMT B-A (RR 1.01, 95% CI 1.00-1.02, p=0.01) and depressive symptoms severity (RR 1.57, 95% CI 1.30-1.89, p<0.01), which were therefore added to a Cox regression model (enter method). Interestingly, only depression (RR 1.55, 95% CI 1.22-1.97, p<0.01) survived as significant risk factor for suicidal behaviour, although a previous suicidal history showed a borderline association (RR 2.78, 95% CI 0.90-8.60, p=0.07) as detailed in table 5.17. below. Although alcohol use was significantly associated with suicidal behaviours risk, given the lack of events in the non-users group, I did not include this variable in the multivariable regression model.

Table 5.16. AESOP: Cox regression analyses for neurocognitive, psychopathological and insight-related variables (n=166)

Risk factor	RR	95% CI	p-value
Neurocognition			
Premorbid IQ	1.02	0.99 - 1.06	0.21
Current IQ	1.00	0.98 - 1.04	0.47
TMT-B-A	**1.01**	**1.00 – 1.02**	**0.01**
Psychopathology			
Positive	1.08	0.93 – 1.24	0.33
Negative	0.93	0.74 – 1.17	0.53
Disorganization	0.84	0.51 – 1.38	0.48
Mania	0.96	0.80 – 1.16	0.68
Depression	**1.57**	**1.30 – 1.89**	**<0.01**
Insight			
Illness recognition	1.14	0.98 – 1.34	0.09
Symptoms relabeling	1.06	0.96 - 1.18	0.25
Treatment compliance	1.30	0.99 – 1.71	0.06
Total insight	1.06	0.99 – 1.13	0.08

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
RR: Relative Risk. CI: Confidence Interval
TMT B-A: Trail Making Test B-A (Reitan, 1958)

Table 5.17. AESOP: Cox regression model

Risk factor		RR	95% CI	p-value
Previous SA	**Present**	**2.78**	**0.90 – 8.60**	**0.07**
	Absent	**1.00**		
TMT B-A		1.00	0.99 – 1.01	0.13
Depression		**1.55**	**1.22 – 1.97**	**<0.01**

Model based on n=116 AESOP patients, including 18 suicide attempters, whom had complete data for all the variables in the model
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SA: Suicide attempts (prior to first presentation/contact)
RR: Relative Risk. CI: Confidence Interval
TMT B-A: Trail Making Test B-A (Reitan, 1958)

5.6. – Discussion

5.6.a. – Main findings

Three main findings emerged from the above results.

First, consistent with findings from chapter 4, I replicated the relationship between illness recognition and total insight at first contact with services and previous SAs. However, previous SA did not survive the multivariable regression models, suggesting that other variables, particularly depression, may explain such a relationship.

Second, with regard to the follow-up analyses, in keeping with my postulations, although the three insight dimensions behaved as risk factors of suicidal behaviour (bivariate analyses), the associations did not reach statistical significance. However, these non-significant associations may have been due to insufficient statistical power (75% for insight variables), particularly taking into account that illness awareness, symptom relabeling and total insight showed trends at a borderline significance ($p<0.1$ but > 0.05). On the other hand, these negative results may be reliable and therefore confirm my hypotheses. Given this uncertainty, I decided to merge this cohort of FEP patients with those presented in chapter 4 from the GAP study, which forms the context for chapter 6.

Third, I replicated the role of previous SA and depressive symptom severity in predicting further suicidal events, whilst taking into account the time to such suicidal events. In addition, a general measure of executive functions such as the TMT B-A was found to be associated with risk of suicidal behaviour in the bivariate analyses (the poorer the cognitive performance, the higher the risk), although this association did not survive the multivariable regression models.

5.6.b. – Insight levels at baseline are influenced by suicidal antecedents

Those patients who had made suicide attempts prior to first presentation to services were found to have significantly greater levels of illness awareness and total insight than non-suicidal subjects. These results were in full alignment with chapter 4 and my previous first author publication (Lopez-Morinigo et al., 2014a).

In addition, consistent with the multidimensionality of insight proposed by David (David, 1990), different predictors were found for each insight dimension which would provide further support for such a model (for a review, see Amador & David, 2004).

More specifically, in line with previous (Wiffen et al., 2012; Mintz et al., 2003; Parellada et al., 2011; McEvoy et al., 2006), but not all (Markova, 2005) studies, I replicated the association of being a female with greater levels of insight, although in this sample the differences were only significant for symptom relabelling and total insight. Also, those patients with higher levels of education had higher levels of insight, particularly in terms of symptom relabelling and total insight, which is consistent with a previous report from our group (Wiffen et al., 2010). This finding also links with employment since those who were unemployed scored lower on insight subscales, namely illness awareness and total insight, than employed people (although this was not statistically significant). However, previous research in this area is scanty (Lysaker & Bell., 1994). In addition, consistent with chapter 4, white patients had significantly higher levels of insight than those of a Black ethnicity, which is in line with previous literature (Johnson & Orrell, 1995; Goldberg et al., 2001; Morgan, 2003), although a previous London-based study by our group in the 90s had failed to show this association (David et al., 1995).

In keeping with chapter 4, an inverse relationship between insight and DUP was replicated (Pek et al., 2006; Saravanan et al., 2010; Cuesta et al., 2011), i.e. the longer the DUP, the poorer the insight at first presentation, although these associations did not reach statistical significance. Again, this cross-sectional association did not allow me to infer causality conclusions. Indeed, both directions of causality are plausible. Thus, poor insight may delay receiving proper (psychiatric) care, thus increasing the DUP. Equally, a more prolonged DUP results in more severe psychotic symptoms at first contact with services, hence poorer insight levels at that point (Drake et al., 2000).

Of relevance to the purposes of this investigation, I replicated the association of depressive symptoms severity with awareness of having a mental illness, treatment

compliance and total insight (Peralta et al., 1998; Mintz et al., 2003; Cooke et al., 2005; Lincoln et al., 2007; Nair et al., 2014; Belvederi et al., 2015). As detailed in chapter 4 (sections 4.6.c.), both directions of causality are possible. The so-called 'demoralization syndrome' (Drake, 1986; Restifo et al., 2009), posits that gaining awareness of negative events such as (mental) illnesses leads patients to depression (and even suicidality), and the 'depressive realism' account (see Ghaemi & Rosenquist, 2004 for a review), which argues that those depressed patients are more likely to recall such negative events, thus showing greater insight at the time of the assessment. Indeed, those participants with suicidal antecedents also presented with more severe depressive symptoms at the study inception, while other psychopathological domains did not significantly differ across groups with/without suicidal history.

In contrast to chapter 4, although consistent with previous research on 'the cognitive basis of insight in psychosis' (Amador et al., 1991; Morgan & David, 2004; Aleman et al., 2006; Ayesa-Arriola et al., 2011; David et al., 2012; Nair et al., 2014), both general cognition (i.e. 'current' IQ as measured by the WAIS) and executive functions, which were evaluated by the TMT B-A, predicted insight levels at first presentation with the exception of treatment compliance. These results were also in line with two previous FEP studies from our group (Morgan et al., 2010b; Wiffen et al., 2012) and a previous meta-analysis (Aleman et al., 2006).

5.6.c. – Insight dimensions did not predict suicide risk over the follow-up

In keeping with my hypotheses, over the 10-year follow-up no insight dimension was significantly associated with risk of suicidal behaviors. However, the RRs (>1) suggest that insight may still be a risk factor for suicide, which may not have been demonstrated due to insufficient statistical power to investigate this. Indeed, with the exception of symptom relabeling, illness recognition, treatment compliance and total insight showed borderline associations with suicidal risk ($p<0.1$ but >0.05). These results replicated those from chapter 4, including the previously reported tautological link between suicidal history, insight levels at first presentation and risk of future suicidal acts, which is in full agreement with previous literature both on schizophrenia (Hawton et al., 2005) and FEP (Challis et al., 2013), as previously postulated (chapter 2, section 2.5) based on my literature review (Lopez-Morinigo et al., 2012) and more recent studies (Yan et al., 2013; Pijnenborg et al., 2013; Barrett et al., 2015).

However, given the relatively limited statistical power (75% for insight variables, see section 5.4.d.1), a type 2 error cannot be excluded. I addressed this limitation by merging these two FEP cohorts (Chapters 4 and 5), which is explained in chapter 6.

5.6.d. – Predictors of suicidal behaviour over the follow-up

In line with previous literature on suicide in psychosis (Hu et al., 1991; De Hert et al., 2001; Sinclair et al., 2004; Hawton et al., 2005; Tarrier et al., 2006; Reutfors et al., 2009; Bakst et al., 2010; Dutta et al., 2010; Pompili et al., 2011; Challis et al., 2013; Björkenstam et al., 2014), including two recent meta-analyses (Large et al., 2011; Challis et al., 2013) and chapter 3 of this thesis, suicidal history was found to be the strongest predictor of future suicidal events in early psychosis. In addition, alcohol use (in comparison to non-use), executive functions (as measured by the TMT B-A) and depressive symptoms severity predicted risk of suicidal behaviour over the 10-year follow-up period.

Drinking alcohol abusively and using recreational drugs have been consistently linked with an increased suicide risk in the general population (see Hawton & van Heeringen., 2009). However, mixed results have been reported with regard to alcohol and suicide risk both in schizophrenia (Hawton et al., 2005) and FEP (Challis et al., 2013), while drugs use was consistently found to increase the risk (Hawton et al., 2005; Challis et al., 2013). The above

results concerning the role of alcohol use in suicide risk in this FEP cohort suggest that, given the high number of alcohol 'users', full abstinence may represent a protective factor for suicide in psychosis, although further replication studies are needed.

Mixed findings have been reported with regard to neurocognition and suicide risk in psychosis (Andersson et al., 2008, Webb et al., 2011; Potkin et al., 2003; Barrett et al., 2011; see Hor & Taylor, 2010 for a general review). In line with my results, cognitive impairment has been reported to reduce suicide risk in patients with schizophrenia spectrum disorders (Fenton et al., 1997; De Hert et al., 2001). Hence, long-term studies of FEP cohorts are needed in this area, including the administration of comprehensive neurocognitive assessments over the course of the illness.

Some negative results from this chapter deserve a comment. Thus, contrary to previous research (e.g. Tsuang, 1978; Osby et al., 2000; Qin & Nordentoft, 2005; Palmer et al., 2005; Limosin et al., 2007; Osborn et al., 2008; Dutta et al., 2010; Barrett et al., 2010a; Barrett et al., 2010b) and the findings presented in chapter 4, I failed to replicate a significant association between age at first presentation and risk of suicidal behaviours, although the tendency was that younger subjects at first contact with mental health services had a higher risk of suicidal behaviours. Of concern, this non-significant association of early age at first presentation with increased suicide risk may be due to limited statistical power. Similarly, the association of living alone with an increased suicide risk in psychosis (Hawton et al., 2005; Challis et al., 2013), although replicated in this sample, did not reach significance.

Figures 5.4 and 5.5, below, represent the model tested in this thesis and the model based on this chapter results, respectively.

Figure 5.4. Hypothesised model to be tested in this thesis

Red arrows increase risk and green arrows show lower risk

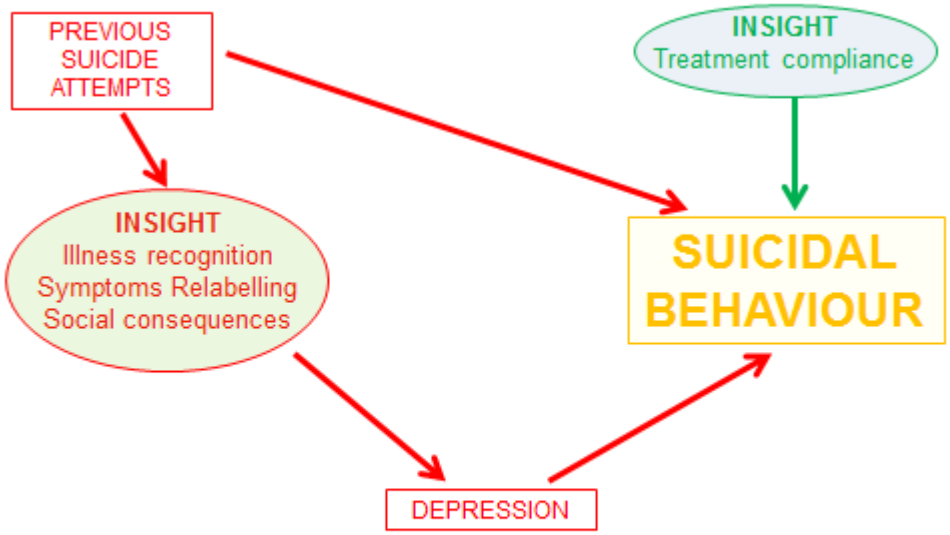
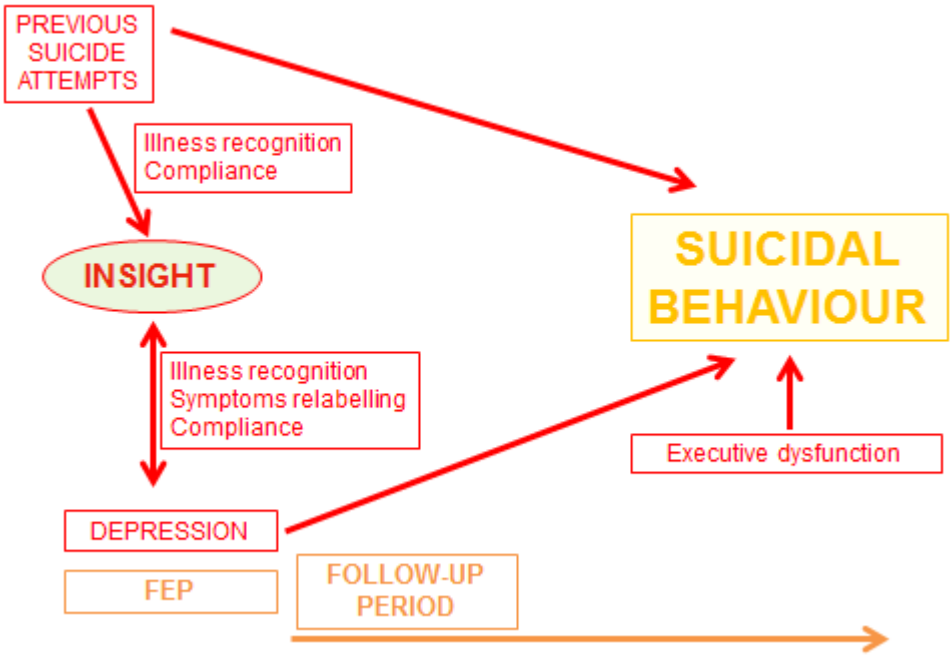


Figure 5.5. Model based on the AESOP cohort results



5.6.e. – Strengths and limitations

While I included a large cohort of FEP patients, which was part of the AESOP study, including a long follow-up (median: 10 years), the statistical power calculations detailed in section 5.4.d.1. suggest that a potential type 2 error cannot be excluded. This led me to merging both London-based FEP cohorts, namely GAP (chapter 4) and AESOP (this chapter) as explained in chapter 6.

In addition, further limitations should be taken into account when drawing conclusions from the above results. First, other non-tested variables might contribute to predicting insight such as premorbid personality (Lysaker et al., 1999; Campos et al., 2011; Cuesta et al., 2011; Ritsner & Blumenkrantz, 2010) and neuroanatomical correlates (Morgan et al., 2010; David et al., 2012). Second, examiners were not blind to other scales such as the PANSS, which might bias the insight assessment (Campos et al., 2011). Third, our cross-sectional assessment of insight did not permit to the investigation of insight changes over the course of the illness (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011; Ayesa-Arriola & Lopez-Morinigo et al., 2014) in relation to suicide risk. Also, demographic variables related to suicide risk such as marital and living status may have changed over the study period. Hence, the link between demographic data at baseline and suicide risk over such a prolonged follow-up should be taken with caution.

5.7. – Chapter summary

Although the findings from this chapter suggest that, consistent with the hypotheses, insight levels were not significantly associated with risk of suicidal behaviors over the early stages of the psychotic illness; these negative results may conceivably have been due to limited statistical power.

As a result, in the next chapter (Chapter 6), I will present the results from analyzing a merged cohort of FEP patients from the GAP (see chapter 4) and AESOP studies (the present chapter), which is detailed in the methods sections (Chapter 6, section 6.4).

Chapter 6 – Suicidal behaviour in early psychosis. Findings from the GAP-AESOP combined cohort of first-episode psychosis patients

6.1. – Introduction

This chapter describes the predictors of suicidal behaviour in a large cohort of first-episode psychosis (FEP) subjects from two sites in the UK (London and Nottingham). More specifically, this cohort of FEP patients was the result of combining the samples presented in chapter 4 (from the GAP study) and 5 (from the AESOP study). In particular, the role of three insight dimensions, namely recognition of having a mental illness, symptom relabelling and awareness of the need for treatment, in suicidal acts, which encompasses suicide attempts and suicide completions, over a prolonged follow-up (7 year median), was investigated. Also, multivariable regression models were built in order to investigate the above associations whilst controlling for a range of demographic and clinical variables which may mediate/confound the relationship between insight dimensions and risk of suicidal behaviours in early psychosis.

6.2. – Background

As detailed in chapters 2, 4 (section 4.2.) and 5 (section 5.2.), the role of insight dimensions in suicidal behaviour in FEP patients remains unclear (Lopez-Morinigo et al., 2012), which may have crucial clinical implications in the development of suicide prevention measures focused on insight management from first presentation.

Although this research question was investigated in chapters 4 and 5 with two cohorts of FEP subjects, the statistical power was limited (ranging from 62.5% to 75.1%), which may have resulted in false negative results. Given that the main hypothesis of this thesis was that insight dimensions are *not* a risk factor for suicide in early psychosis, the fact that the above negative results from chapters 4 and 5 might have been due to insufficient statistical power would not allow me to draw definitive conclusions. In order to address this issue, I decided to merge both UK-based FEP cohorts and analyse the results from this larger (and statistically more powerful) sample concerning the above research question.

6.3. – Aims and Objectives

6.3.a. – Descriptive aims and objectives

- To describe the distribution of insight dimensions according to the outcome of suicidal behaviours, including both suicide attempts and suicide completions.

6.3.b. – Analytical aims and objectives

- To investigate whether there is an association between a history of suicidal behaviours before first presentation with psychosis and insight levels at that point.
- To adjust the above analyses for a set of potential confounders in order to determine independent predictors of insight at baseline, including the role of previous suicidal history.
- To calculate the case fatality of this FEP sample over the 7-year follow-up period.
- To identify the risk factors associated with suicidal behaviours in a FEP cohort over a 7-year follow-up period.
    - And to determine whether there is an association of insight levels with risk of suicidal behaviours over the 7-year follow-up period.
- To test for potential interactions between insight dimensions and other clinical and demographic variables related to risk of suicidal behaviour.
- To formulate a model, based on a multivariable Cox Regression analysis of the above baseline variables, including insight dimensions, for predicting suicidal behaviours over the 7-year follow-up period.

6.4. – Methods

6.4.a. – Sample, baseline assessment and follow-up procedure

The sample for this chapter came from two FEP studies, namely the Genetics and Psychosis (GAP) and the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP). The methodology of both studies is detailed in chapters 4 (section 4.4) and 5 (section 5.4), respectively.

In brief, it should be noted that both studies aimed to recruit all the incident cases presenting with a FEP (F10-F29 and F30- F33 in ICD-10) to the South London and Maudsley NHS Foundation Trust over 1997-1999 (AESOP) and 2004-2010 (GAP), although a small proportion of AESOP patients were recruited in Nottingham. Also, inclusion and exclusion criteria in AESOP and GAP studies were very similar as follows:

Inclusion criteria:

a) age between 16 and 65 years (both studies)

b) resident within tightly defined catchment areas in Nottingham (only AESOP) or south-east London (GAP and AESOP)

c) presence of a first episode of psychosis, namely F10-F29 and F30- F33 codes in ICD-10 within the time frame of the study (both studies).

Exclusion criteria:

a) evidence of an organic cause of psychosis (both studies)

b) drug-induced psychosis (both studies)

c) IQ less than 50 (both studies)

d) poor fluency of English (both studies)

Participants in both studies provided written informed consent and both AESOP and GAP projects obtained ethical approval from the Local Research Ethics Committees.

In order to ascertain suicidal behaviours over the follow-up, there were some minor differences between GAP and AESOP studies. In particular, GAP patients were traced by

contacting the patient via a phone call and/or a letter and contacting the GP. However, AESOP patients who were in contact with mental health services at approximately 10 years were contacted via the clinical teams and invited to participate in the study. For those who were not under mental healthcare, up to two letters were sent to their last known address inviting them to participate. In addition, researchers made a maximum of three visits to the address (morning, afternoon and evening) to make initial contact. For those who had moved address, and for whom GP details were available, an invitation letter was sent to the GP.

Clinical records were used in both studies to collect information on outcome variables, including suicidality where available. With regard to all-cause mortality data, including suicide, similar methods were used in both AESOP and GAP studies. Specifically, a person-tracing procedure conducted on behalf of the teams by the Office for National Statistics (ONS), which in the UK records the official cause of death by using ICD-10 codes.

6.4.b. – Measures

6.4.b.1. – Premorbid, sociodemographic and clinical variables

The following sociodemographic variables collected used in this combined analysis: sex, age at admission (GAP) or first contact with services (AESOP), level of education, living status ("alone" vs. "other"), employment status ("employed", "student" or "unemployed"), cannabis and alcohol use (yes/no) and abuse/dependence (yes/no). The duration of untreated psychosis (DUP) was measured in a slightly different manner in both studies. While GAP used the Nottingham Onset Schedule (Singh et al., 2005) to estimate DUP from medical records, which was defined as the time from the date of the first continuous psychotic symptom (lasting at least a week) to the date of commencing on antipsychotic medication (having taken 75% of doses within the following month), the AESOP study considered the time from the onset of psychosis (first psychotic symptom) to first contact with services.

6.4.b.2. – Insight

The Schedule for Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997) was used to evaluate insight in both studies (see sections 4.4.b.2 and 5.4.c.4).

Since both GAP and AESOP studies used the same insight measurement, I found it appropriate to merge both samples in this chapter.

6.4.b.3. – Neurocognitive tests

The same neurocognitive tests were used in both studies, namely the National Adult Reading Test (NART) (Nelson & Willison, 1991), the short version of the Wechsler Adult Intelligence Scale Revised (WAIS-R, Wechsler, 1981) and the Trail Making Test (Reitan, 1958), which assessed premorbid and current IQ and frontal functions, respectively. See further details about the neurocognitive assessments in sections 4.4.b.3. and 5.4.c.2.

6.4.b.4. – Psychopathological symptoms

In the GAP study five psychopathological dimensions were measured with the Positive and Negative Symptoms Scale for Schizophrenia (PANSS, Kay et al., 1987) based on a previous systematic review of PANSS factor analyses (Wallwork et al., 2012): positive, negative, disorganization, mania and depression.

In keeping with this, five symptomatic dimensions emerged from a previous factor analysis with an overlapping AESOP sample (Demjaha et al., 2009), although it should be noted that the AESOP study used the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO, 1992), particularly the SCAN's Item Group Checklist (IGC) algorithm, to evaluate psychopathological symptom severity.

Given the different distribution of scores for these dimensions across studies, as expected, groups (present vs. absent) were created for each symptom dimension. In the AESOP subsample, for each symptom domain, scores of 0 designated absence of the symptom, while scores of 1 or greater values than 1 indicated presence. For the GAP cohort, patients' symptoms were rated as 'absent' if all the PANSS items included in each psychopathological dimension had scores of 1 or 2, while greater scores (≥3) indicated presence of the symptom.

6.4.b.5. – Suicide attempts information

There were no differences in collecting information on suicidal behaviours between the GAP and AESOP studies (see sections 4.4.b.5 and 5.4.c.5, respectively).

6.4.c – Statistics

For the purposes of this chapter, I performed the same statistical analyses as in chapters 4 and 5 (see sections 4.4.c. and 5.4.d. for further details) with the Statistical Package for Social Science version 22.0 (SPSS Inc., Chicago, IL, USA).

Firstly I explored differences in demographic and clinical variables between patients with/without suicidal history and I explored predictors of each insight dimension through hierarchical linear regression models. Secondly, survival analyses were carried out to investigate time from first contact to the first suicide attempt (or suicide completion as appropriate) or the censoring point, i.e. either the date on which the patient was last known to be alive or the end of the follow-up study period, whichever came sooner. Specifically, survival in relation to baseline insight variables, whilst adjusting the analyses for potential mediating/confounding demographic and clinical variables through multivariable Cox-Regression (Cox, 1972) models were built up. The analyses were two-tailed and significance level was set at 5%.

6.4.c.1. – Power calculations

The *stpower logrank* command of STATA 11.0 for Windows (StataCorp LP, USA) was used to carry out the power calculations

As alluded to in chapters 4 (section 4.4.c.1) and 5 (section 5.4.d.1), based on previous FEP studies, it was expected that at the end of the follow-up (median=7 years in this study) at least 20% of the initial sample size will have made one suicide attempt (e.g. Robinson et al., 2010), including 2-5% of suicides (Dutta et al., 2010; Palmer et al., 2005). Given that the mean SAI-E score for FEP patients is around 13/28 with a standard deviation of around 6 (e.g. Morgan et al., 2010), a difference of 2 points (e.g. 13 vs 15) between suicide attempters and non-attempters, which is considered to be clinically meaningful (Kemp & David, 1998), is equivalent to an effect size of 0.33 with a two-tailed alpha set at 5%. Under these assumptions, I would have 90.8% power to detect this difference in the SAI-E between groups in this FEP cohort (n=297).

6.5. – Results

6.5.a. – Descriptive analyses

The demographic and clinical characteristics, including symptom-related variables, of the whole sample and differences between subsamples are presented in table 6.1. and table 6.2., below. There were no significant differences in age at first contact and gender, although the GAP cohort included more subjects with no qualifications, of non-white origin and a greater proportion of patients with a diagnosis of schizophrenia spectrum disorders who also had a higher prevalence of lifetime drug use.

Also, GAP patients were more likely to have suicidal antecedents prior to first presentation than those from the AESOP study.

In terms of psychopathology, AESOP and GAP participants significantly differed, as expected, since different instruments were used in both cohorts.

Table 6.1. Demographic and clinical characteristics of the whole sample (N=293) and differences between AESOP (n=181) and GAP patients (n=112)

	Data available N (%)	Total sample	AESOP n = 181 (61.8%)	GAP n = 112 (38.2%)	Statistic	p-value
Age at first contact, years:	276 (94.2)	30.5 ± 10.5	31.3 ± 11.2	29.4 ± 9.2	t=1.5	0.13
Gender, males	293 (100)	175 (59.4)	101 (55.8)	73 (65.2)	X^2 =2.5	0.11
Level of education	285 (97.3)					
No qualifications		73 (25.6)	55 (31.4)	18 (16.4)	X^2 =8.0	<0.01
GCSE		70 (24.6)	47 (26.8)	23 (20.9)	X^2 =1.3	0.26
Further		93 (31.7)	51 (29.1)	42 (38.2)	X^2 =2.5	0.11
University		49 (16.7)	22 (12.6)	27 (24.5)	X^2 =6.8	0.01
Living alone	279 (95.2)	92 (32.9)	52 (30.9)	40 (36.0)	X^2 =0.8	0.38
Unemployed	285 (97.3)	147 (51.6)	78 (44.6)	69 (62.7)	X^2 =8.9	<0.01
Ethnicity	292 (99.7)					
White		130 (44.5)	101 (55.8)	29 (26.1)	X^2 =24.5	<0.01
Black		110 (37.5)	61 (33.7)	49 (44.1)	X^2=3.2	0.07
Other		52 (17.7)	19 (10.5)	33 (29.7)	X^2 =17.4	<0.01
DUP: days, median	277 (94.5)	48	49.5	42	U	0.96
Diagnosis (ICD-10)	292 (99.7)					
Schizophrenia		204 (69.9)	118 (65.2)	86 (77.5)	X^2=4.9	0.03
Mania		47 (16.1)	31 (17.1)	16 (14.4)	X^2=0.4	0.54
Depression		41 (14.0)	32 (17.7)	9 (8.1)	X^2= 0.3	0.57
Alcohol use	270 (92.2)	220 (81.5)	152 (84.4)	68 (75.5)	X^2=3.1	0.08
Drugs use	287 (98.0)	184 (64.1)	103 (58.8)	81 (72.3)	X^2=5.4	0.02
Suicidal history	274 (93.5)	38 (13.9)	16 (9.9)	22 (19.6)	X^2= 5.4	0.02
Positive	265 (90.4)	211 (79.6)	131(83.9)	80 (73.4)	X^2=4.4	0.03
Negative	265 (90.4)	143 (53.9)	79 (50.6)	64 (58.7)	X^2=0.5	0.19
Disorganization	265 (90.4)	128 (48.3)	57 (36.5)	71 (65.1)	X^2=21.0	<0.01
Mania	265 (90.4)	113 (42.6)	84 (53.8)	29 (26.6)	X^2=19.4	<0.01
Depression	265 (90.4)	151 (56.9)	70 (44.9)	81 (74.3)	X^2=22.7	<0.01

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses. GAP: Genetics and Psychosis Study
GCSE: General Certificate of Secondary Education
DUP: Duration of untreated psychosis

Table 6.2., below, shows the mean scores on insight dimensions, psychopathological and neurocognitive variables in the whole sample and differences between both cohorts. In particular, although total insight scores did not significantly differ between AESOP and GAP samples, some dimensions, namely illness awareness and compliance were significantly greater in AESOP patients. In addition, AESOP patients were found to have a higher premorbid IQ (verbal, performance and full), although no further neurocognitive differences emerged from the analyses.

Table 6.2. GAP-AESOP combined cohort: Insight scores and neurocognitive variables

	Data availability N (%)	Total sample	AESOP	GAP	Statistic	p-value
Insight scores						
Recognition	***293 (100)***		***n=181***	***n=112***		
		6.2 ± 3.0	**6.0 ± 3.0**	**5.0 ± 3.3**	**t=2.8**	**p<0.01**
Relabelling	*284 (96.9)*		*n=181*	*n=103*		
		4.9 ± 3.5	4.7 ± 3.6	4.9 ± 3.4	t=-0.6	p=0.57
Compliance	***265 (90.4)***		***n=157***	***n=108***		
		3.2 ± 1.6	**3.2 ± 1.5**	**3.8 ± 1.8**	**t=1.4**	**p=0.01**
Total Insight	*257 (87.7)*		*n=157*	*n=100*		
		14.1 ± 6.6	13.6 ± 3.6	13.6 ± 7.3	t=-0.0	p=0.99
Premorbid IQ	*237 (80.9)*		***n=147***	***n=90***		
Verbal		**93.3 ± 13.3**	**96.6 ± 13.5**	**87.9 ± 11.3**	**t=5.3**	**<0.01**
Performance		**96.8 ± 12.3**	**98.1 ± 13.0**	**94.7 ± 10.6**	**t=2.1**	**0.03**
Full		**93.8 ± 18.5**	**95.9 ± 21.7**	**90.5 ± 10.6**	**t=2.5**	**0.01**
IQ (WAIS-III)	*242 (82.6)*		*n=150*	*n=92*		
		86.8 ± 28.8	85.8 ± 30.8	88.4 ± 25.3	t=-0.7	0.50
TMT-A (seconds)	*239 (81.6)*		*n=147*	*n=92*		
		46.0 ± 27.4	45.4 ± 30.8	46.9 ± 20.9	t=-0.4	0.67
TMT-B (seconds)	*230 (78.5)*		*n=144*	*n=86*		
		108.6 ± 71.3	102.1 ± 69.2	119.5 ± 74.0	t=-1.8	0.07
TMT-B-A (seconds)	*224 (76.4)*		*n=138*	*n=86*		
		65.1 ± 53.2	60.9 ± 46.4	71.8 ± 62.4	t=-1.4	0.16

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
IQ; Intelligence Quotient. WAIS: Wechsler Adult Intelligence Scale, revised (Wechsler, 1981).
TMT: Trail Making test (Reitan, 1958)

6.5.b. – Baseline differences between subjects with/without suicidal history

Two hundred and ninety-three subjects were included in this cohort. The sociodemographic and clinical characteristics of the whole sample and differences between those with /without suicidal history prior to first contact with services are presented in Tables 6.3., 6.4. and 6.5., below.

Table 6.3. GAP-AESOP combined cohort: Demographic and clinical characteristics and differences between patients with/without suicidal history

	With previous SA n=38	Without previous SA n=236	Statistic	p-value
Age at first contact, years	29.3 ± 8.8	30.8 ± 10.7	t=-0.8	0.40
Gender, males	21 (55.3)	138 (58.5)	X^2 =0.1	0.71
Level of education				
No qualifications	13 (34.2)	56 (23.9)	X^2 =1.8	0.18
GCSE	9 (23.7)	58 (24.8)	X^2 =0.0	0.88
Further	9 (23.7)	78 (32.8)	X^2 =1.4	0.24
University	7 (18.4)	42 (17.9)	X^2 =0.0	0.94
Unmarried	22 (59.4)	165 (72.0)	X^2 =2.4	0.12
Living alone	16 (42.1)	74 (31.5)	X^2 =1.7	0.20
Unemployed	18 (47.3)	120 (51.3)	X^2 =0.2	0.65
Ethnicity				
White	19 (50.0)	102 (43.4)	X^2 =0.6	0.45
Black	9 (23.7)	92 (39.1)	X^2 =3.3	0.07
Other	10 (26.3)	41 (17.4)	X^2 =1.7	0.19
DUP: days, median	127.5	45	U	0.37
Diagnosis (ICD-10)				
Schizophrenia	25 (15.7)	164 (69.5)	X^2 =0.0	0.81
Mania	3 (8.1)	43 (18.2)	X^2 =2.3	0.13
Depression	**9 (24.3)**	**29 (12.3)**	**X^2 =3.9**	**0.05**
Alcohol use	28 (87.5)	178 (81.3)	X^2 =0.7	0.39
Drugs use	25 (67.5)	146 (62.9)	X^2 =0.3	0.59
Positive	29 (78.4)	176 (79.6)	X^2 =0.0	0.86
Negative	**26 (70.3)**	**111 (50.2)**	**X^2 =5.1**	**0.02**
Disorganization	17 (45.9)	107 (48.4)	X^2 =0.1	0.78
Mania	11 (29.7)	96 (43.4)	X^2 =2.4	0.12
Depression	**30 (81.1)**	**118 (53.4)**	**X^2 =9.9**	**<0.01**

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SA: Suicide attempts (prior to first contact). GCSE: General Certificate of Secondary Education
DUP: Duration of untreated psychosis

With regard to insight dimensions, those subjects with suicidal history before first presentation to services had higher insight scores than non-suicidal patients as detailed in table 6.4., below.

Table 6.4. GAP-AESOP combined cohort: mean Insight level differences between those with/without suicidal history

	With previous SA	Without previous SA	statistic	p-value
Awareness of illness	**6.8 ± 2.5**	**5.4 ± 3.2**	**t=3.0**	**<0.01**
Symptoms relabeling	**5.9 ± 3.2**	**4.6 ± 3.6**	**t=2.1**	**0.03**
Compliance	**4.2 ± 1.6**	**3.4 ± 1.7**	**t=2.8**	**0.01**
Total insight	**16.9 ± 5.8**	**13.1 ± 6.9**	**t=3.1**	**<0.01**

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
SA: Suicide attempts (prior to first presentation/contact)

Neurocognitive differences between those with/without suicidal history are shown in table 6.5. below, all of which were non-significant.

Table 6.5. GAP-AESOP combined cohort: Neurocognitive differences between those with/without suicidal history

	Suicidal patients	non-suicidal patients	statistic	p-value
Premorbid IQ	*n=31*	*n=192*		
Verbal	92.2 ± 13.7	93.9 ± 13.3	t=-0.6	0.51
Performance	97.3 ± 11.3	97.3 ± 12.3	t=-0.0	0.99
Full	94.3 ± 13.5	95.3 ± 13.6	t=-0.3	0.72
Current IQ	*n=30*	*n=196*		
	91.9 ± 14.8	86.6 ± 31.4	t=0.9	0.36
Executive functions	*n=29*	*n=180-195*		
TMT-A	44.8 ± 20.0	44.9 ± 26.9	t=-0.0	0.98
TMT-B	108.9 ± 65.2	106.9 ± 72.9	t=0.1	0.89
TMT B-A	66.7 ± 57.0	547.7 ± 54.2	t=0.2	0.85

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
IQ; Intelligence Quotient. WAIS: Wechsler Adult Intelligence Scale, revised (Wechsler, 1981).
TMT: Trail Making Test (Reitan, 1958)

6.5.c. – Bivariate analyses: relationships between insight dimensions and baseline demographic and clinical characteristics of the sample

Exploratory analyses investigated potential relationships between insight (as the dependent variable) and a wide range of baseline demographic variables. In particular, no significant differences in insight scores emerged from between-group comparisons with regard to age at first contact, marital and living status.

However, females were found to have higher levels of all insight dimensions than males, although for compliance this difference was not significant. Also, symptom relabelling and total insight scores were significantly greater in those with higher education levels compared with those with no qualifications. In addition, employed participants showed significantly higher levels of all insight dimensions than those who were unemployed, although the difference did not reach statistical significance for compliance.

Finally, white patients had significantly greater insight scores (all dimensions and total insight) than black patients and 'other' ethnicities, although treatment compliance differences were of borderline significance ($p=0.06$). See table 6.6., below, for further details.

Table 6.6. GAP-AESOP combined cohort: Relationships between baseline demographic data and insight scores

	Recognition	Relabelling	Compliance	Total insight
Age at first contact	*n=276*	*n=267*	*n=252*	*n=244*
	r=-0.06	**r=-0.14**	r=-0.01	r =-0.09
	p=0.30	**r=0.02**	p=0.85	p = 0.15
Gender	*n=293*	*n=284*	*n=265*	*n=257*
Males	**5.2 ± 3.2**	**4.3 ± 3.2**	3.3 ± 1.7	**12.5 ± 6.8**
Females	**6.3 ± 3.0**	**5.5 ± 3.8**	3.6 ± 1.6	**15.2 ± 6.9**
	t=-2.9, p<0.01	**t=-2.8, p=0.01**	t=-1.5, p=0.14	**t=-3.1, p<0.01**
Level of education	*n=285*	***n=276***	*n=259*	***n=251***
No qualifications	5.3 ± 3.3	**3.9 ± 3.4**	3.3 ± 1.7	**12.3 ± 6.9**
≥ GCSE	5.8 ± 3.1	**5.1 ± 3.5**	3.5 ± 1.6	**14.2 ± 6.8**
	t=-1.2, p=0.23	**t=-2.5, p=0.01**	t=-0.8, p=0.42	**t=-2.0, p=0.04**
Marital status	*n=273*	*n=267*	***n=249***	*n=243*
Unmarried	5.5 ± 3.1	4.8 ± 3.6	**3.3 ± 1.7**	13.5 ± 7.2
Married	5.9 ± 3.0	4.8 ± 3.2	**3.8 ± 1.4**	14.3 ± 5.8
	t=-0.9, p=0.33	t=0.1, p=0.88	**t=-2.0, p=0.04**	t=-0.8, p=0.39
Living status	*n=279*	*n=270*	*n=254*	*n=246*
Alone	5.6 ± 3.2	4.8 ± 3.5	3.4 ± 1.7	13.9 ± 7.3
With others	5.6 ± 3.1	4.8 ± 3.5	3.5 ± 1.7	13.5 ± 6.7
	t=0.1, p=0.93	t=0.1, p=0.94	t=-0.5, p=0.60	t=0.3, p=0.73
Employment status	***n=285***	*n=277*	*n=260*	***n=252***
Unemployed	**5.2 ± 3.3**	**4.3 ± 3.5**	3.3 ± 1.7	**12.6 ± 7.2**
Employed	**6.2 ± 2.9**	**5.3 ± 3.5**	3.6 ± 1.6	**14.9 ± 6.3**
	t=-2.7, p=0.01	**t=-2.3, p=0.02**	t=-1.8, p=0.06	**t=-2.8, p=0.01**
Ethnicity	*n=292*	*n=284*	*n=264*	*n=256*
White	**6.5 ± 2.9**	**5.3 ± 3.5**	3.7 ± 1.6	**15.1 ± 6.6**
Black	**4.9 ± 3.2**	**4.1 ± 3.4**	3.1 ± 1.7	**12.0 ± 6.7**
Others	5.0 ± 3.1	4.9 ± 3.5	3.4 ± 1.8	13.3 ± 7.5
	F=9.8 p<0.01	**F=3.5, p=0.03**	F=2.7, p=0.06	**F=5.6, p<0.01**

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
GCSE: General Certificate of Secondary Education

With regard to baseline clinical characteristics of the sample such as DUP, diagnosis and alcohol and illicit drugs (use vs. non-use), several significant differences emerged from the bivariate analyses which are shown in table 6.7., below.

DUP showed a negative significant association with both relabelling and total insight.

In terms of diagnosis, those subjects with psychotic depression showed significantly greater levels of illness awareness than those with schizophrenia spectrum disorders and mania with psychosis.

In addition, alcohol drinkers had greater levels of symptoms relabelling than those without a history of alcohol consumption.

Other non-significant differences are shown in table 6.7., below.

Table 6.7. GAP-AESOP combined cohort: Relationships between insight dimensions and clinical characteristics

	Recognition	Relabelling	Compliance	Total Insight
DUP	*n*=277	*n*=268	*n*=253	*n*=245
<48 days	**5.2 ± 3.2**	**4.2 ± 3.4**	**3.2 ± 1.7**	**12.5 ± 6.8**
>48 days	**6.0 ± 3.0**	**5.4 ± 3.6**	**3.7 ± 1.6**	**14.9 ± 6.8**
	t=-2.2 p=0.03	**t=-2.7, p=0.01**	**t=-2.6, p=0.01**	**t=-2.7, p=0.01**
Diagnosis	*n=292*	*n=283*	*n=265*	*n=257*
Schizophrenia	5.3 ± 3.2	4.6 ± 3.5	3.5 ± 1.7	13.2 ± 7.0
Mania	5.3 ± 3.2	4.8 ± 3.5	2.7 ± 1.5	12.4 ± 6.8
Depression	**7.5 ± 2.3**	5.6 ± 3.4	**3.9 ± 1.4**	**16.9 ± 5.3**
	F=9.1, p<0.01	F=1.5, p=0.23	F=5.4, p<0.01	F=5.03, p=0.01
Alcohol	*n=270*	*n=266*	*n=243*	*n=240*
Use	5.9 ± 3.1	**5.0 ± 3.6**	3.5 ± 1.7	14.2 ± 6.9
non-use	5.2 ± 3.2	**3.9 ± 3.0**	3.3 ± 1.7	12.2 ± 6.3
	t=1.5, p=0.13	**t=2.1, p=0.04**	t=0.5, p=0.62	t=1.7, p=0.09
Drugs	*n=287*	*n=278*	*n=259*	*n=251*
Use	5.8 ± 3.2	5.0 ± 3.5	3.5 ± 1.8	14.1 ± 7.2
non-use	5.3 ± 3.1	4.4 ± 3.5	3.3 ± 1.5	12.9 ± 6.5
	t=1.4, p=0.17	t=1.5, p=0.14	t=0.9, p=0.36	t=1.4, p=0.16

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
DUP: Duration of untreated psychosis

In addition, I compared insight levels across groups of psychopathological dimensions (presence vs. absence) as explained in section 6.4.b.3., above. Illness awareness and compliance were significantly higher in those with depression compared with non-depressed patients. Also, compliance was significantly higher in those affected by negative symptoms and lower in manic patients than in non-manic subjects. Symptom relabelling score was significantly lower in those with positive symptoms, while total insight differences across groups did not reach significance.

Table 6.8. GAP-AESOP cohort: Insight dimensions and psychopathological domains

	Recognition *n*=265	**Relabelling** *n*=257	**Compliance** *n*=242	**Total Insight** *n*=235
Positive				
Presence	5.2 ± 3.2	**4.5 ± 3.2**	3.5 ± 1.6	13.4 ± 6.8
Absence	5.9 ± 3.0	**5.9 ± 4.0**	3.3 ± 1.7	14.5 ± 7.5
	t=-0.9 p=0.36	**t=-2.3, p=0.03**	t=1.1, p=0.29	t=-0.9, p=0.35
Negative				
Presence	5.5 ± 3.1	4.8 ± 3.3	**3.7 ± 1.6**	13.9 ± 6.7
Absence	5.7 ± 3.3	4.7 ± 3.8	**3.2 ± 1.7**	13.2 ± 7.3
	t=-0.5, p=0.59	t=0.1, p=0.94	**t=2.8, p=0.01**	t=0.7, p=0.45
Disorganization				
Presence	5.2 ± 3.2	4.7 ± 3.4	3.4 ± 1.7	13.0 ± 6.9
Absence	5.9 ± 3.1	4.8 ± 3.7	3.6 ± 1.6	14.2 ± 6.9
	t=-1.9, p=0.06	t=0.4, p=0.67	t=-1.2, p=0.22	t=-1.3, p=0.20
Mania				
Presence	5.4 ± 3.2	4.5 ± 3.5	**3.2 ± 1.6**	12.9 ± 6.5
Absence	5.7 ± 3.2	4.9 ± 3.6	**3.7 ± 1.7**	14.1 ± 7.2
	t=-0.8, p=0.44	t=-1.1, p=0.29	**t=-2.0, p=0.04**	t=-1.4, p=0.17
Depression				
Presence	**6.0 ± 3.1**	4.8 ± 3.4	**3.8 ± 1.6**	14.7 ± 6.6
Absence	**5.0 ± 3.2**	4.6 ± 3.7	**3.0 ± 1.6**	12.0 ± 7.2
	t=2.7, p=0.01	t=0.5, p=0.61	**t=3.9, p<0.01**	t=2.9, p=0.16

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.

In line with chapters 4 and 5, I explored bivariate correlations of insight levels with neurocognitive variables, which are shown in table 6.9., below, which revealed several significant differences. In particular, illness recognition and symptom relabeling significantly correlated with current IQ and two measures of executive functions such as TMT-A and TMT-B, while no significant associations of compliance with neurocognitive variables emerged from the analyses. Also, total insight score was significantly associated with current IQ and TMT-A.

Table 6.9. GAP-AESOP combined cohort: Correlations of insight dimensions with neurocognitive variables

	Recognition			Relabeling			Compliance			Total Insight		
	n	r	p	n	r	p	n	r	p	n	r	p
Premorbid Verbal IQ	237	0.15	0.02	232	0.16	**0.01**	212	-0.03	0.61	208	0.12	0.09
Premorbid Performance IQ	237	0.10	0.12	232	0.16	**0.01**	212	0.02	0.77	208	0.11	0.10
Full Premorbid IQ	237	0.10	0.11	232	0.11	0.11	212	0.04	0.60	208	0.09	0.21
IQ (WAIS-III)	242	0.17	**0.01**	236	0.15	**0.02**	216	0.09	0.52	211	0.15	**0.02**
TMT-A (seconds)	239	-0.25	**<0.01**	233	-0.19	**<0.01**	215	-0.10	0.12	210	-0.24	**<0.01**
TMT-B (seconds)	230	-0.18	**<0.01**	225	-0.14	**0.03**	205	0.02	0.81	201	-0.14	0.05
TMT B-A (seconds)	224	-0.12	0.07	219	-0.11	0.11	200	0.04	0.56	196	-0.08	0.27

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses.
IQ: Intelligence Quotient. WAIS: Wechsler Adult Intelligence Scale, revised (Wechsler, 1981).
TMT: Trail Making Test (Reitan, 1958)

6.5.d – Regression on recognition of illness

A hierarchical linear regression model ('enter' method) was performed to reassess the association of suicidal history with recognition of illness, whilst adjusting for some variables which had also been associated with illness recognition, such as gender, unemployment, being white, DUP, a diagnosis of depression with psychotic symptoms, two neurocognitive measures (i.e., current IQ and TMT-A) and depressive symptoms severity. As a result, only DUP and depressive symptom severity remained significant predictors of recognition of mental illness in the final model, which accounted for 11% of the variance on illness recognition.

Table 6.10. GAP-AESOP combined cohort: Regression on recognition

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				0.032	0.10
Gender (male)	-0.04	0.25	0.86		
Unemployed	-0.25	0.25	0.33		
White	0.30	0.25	0.23		
Block 2:				0.031	0.01
DUP	**-0.65**	**0.24**	**0.01**		
Block 3:				0.017	0.07
Previous SA	0.48	0.35	0.17		
Block 4:				0.004	0.37
Depression (dx)	0.09	0.38	0.81		
Block 4:				0.003	0.74
Current IQ	0.00	0.00	0.55		
TMT-A	0.00	0.00	0.97		
Block 5:				0.026	0.02
Depressive sym.	**0.58**	**0.25**	**0.02**		
GLOBAL R^2				0.11	

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
DUP: Duration of untreated psychosis. SA: Suicide attempts (prior to first presentation)
dx: diagnosis IQ: Intelligence Quotient. WAIS: Wechsler Adult Intelligence Scale, revised (Wechsler, 1981)
TMT-A: Trail Making Test, task A (Reitan, 1958)
sym: symptoms severity

6.5.e – Regression on relabelling of symptoms

A hierarchical linear regression model ('enter' method) was carried out to reassess the association of suicidal history with symptoms relabelling after controlling for the effects of a set of demographic variables (age at first contact, gender, education level, employment and being white), DUP, alcohol use, two neurocognitive measures such as IQ and TMT-A and positive symptoms severity. Thus, only gender and DUP predicted symptoms relabelling and the model, as a whole, explained up to 18% of the variance on relabelling of symptoms.

Table 6.11. GAP-AESOP combined cohort: Regression on relabelling

	B	SE	p	R^2 Change	p-change
Block 1:				0.105	<0.01
Age	-0.05	0.03	0.08		
Gender (male)	**-1.48**	**0.54**	**<0.01**		
No qualifications	-1.12	0.65	0.08		
Unemployed	0.24	0.53	0.65		
White	0.31	0.55	0.57		
Block 2:				0.021	0.04
DUP (>48days)	**-1.10**	**0.52**	**0.04**		
Block 3:				0.016	0.07
Alcohol use	1.12	0.71	0.12		
Block 4:				0.008	0.19
Previous SA	0.92	0.76	0.26		
Block 5:				0.015	0.20
Current IQ	0.01	0.01	0.39		
TMT-A	-0.01	0.01	0.17		
Block 6:				0.016	0.06
Positive	-1.14	0.60	0.06		
GLOBAL R^2				0.18	

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
DUP: Duration of untreated psychosis
SA: Suicide attempts (prior to first presentation)
dx: diagnosis
IQ: Intelligence Quotient. WAIS: Wechsler Adult Intelligence Scale, revised (Wechsler, 1981)
TMT-A: Trail Making Test, task A (Reitan, 1958)
sym: symptoms severity

6.5.f. – Regression on treatment compliance

DUP, suicidal history, a diagnosis of depression with psychotic features and three psychopathological domains such as negative symptoms, mania and depression were added to the multivariable regression model. Of note, only DUP and two psychopathological domains such as negative and depressive symptom severity remained significant predictors of compliance in the final model, which accounted for just 12% of the variance on treatment compliance (table 6.12 below).

Table 6.12. GAP-AESOP combined cohort: Regression on treatment compliance

	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				0.016	0.06
Unmarried	-0.28	0.23	0.23		
Block 2:				0.018	0.04
DUP	**-0.56**	**0.21**	**<0.01**		
Block 3:				0.022	0.02
Previous SA	0.45	0.30	0.14		
Block 4:				0.005	0.30
Depression (dx)	0.03	0.33	0.94		
Block 4:				0.062	<0.01
Negative	**0.47**	**0.21**	**0.03**		
Mania	-0.30	0.22	0.17		
Depression	**0.57**	**0.23**	**0.01**		
GLOBAL R^2				0.12	

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
DUP: Duration of untreated psychosis
SA: Suicide attempts (prior to first presentation)
dx: diagnosis

6.5.g. – Regression on total insight

A hierarchical linear regression model ('enter' method) was carried out to reassess the association of suicidal history with total insight after controlling for the effects of demographic variables, such as gender, education level (no qualifications vs. higher education), unemployment and being white, a diagnosis of depression with psychotic symptoms (as opposed to all other diagnoses) and two neurocognitive variables (current IQ and TMT-A). Interestingly, only education level (no qualifications), DUP and suicidal history survived the multivariable regression model, which accounted for 19% of the variance on total insight, which is detailed in table 6.13., below.

Table 6.13. GAP-AESOP combined cohort: Regression on total insight

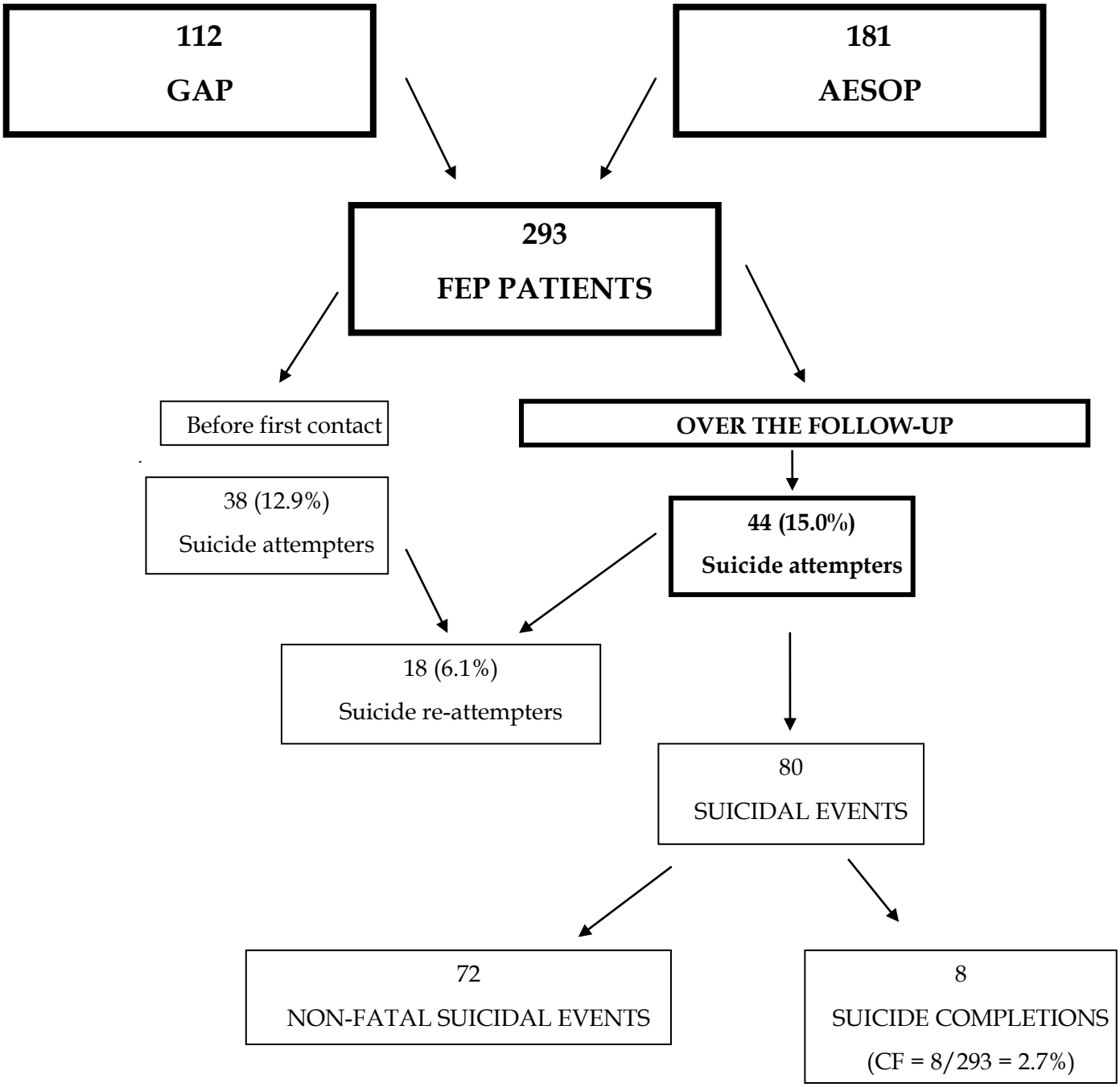
	B	**SE**	**p**	**R^2 Change**	**p-change**
Block 1:				0.112	<0.01
Gender	-2.00	0.99	0.04		
No qualifications	**-2.80**	**1.17**	**0.02**		
Unemployment	-0.47	0.99	0.64		
White	1.48	1.02	0.15		
Block 2:				0.024	0.02
DUP	**-2.27**	**0.96**	**0.02**		
Block 3:				0.026	0.02
Previous SA	**3.23**	**1.37**	**0.02**		
Block 4:				0.010	0.14
Depression (dx)	2.03	1.46	0.17		
Block 4:				0.017	0.14
Current IQ	0.01	0.02	0.72		
TMT-A	-0.03	0.02	0.07		
GLOBAL R^2				0.19	

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
DUP: Duration of untreated psychosis
SA: Suicide attempts (prior to first presentation/contact)
dx: diagnosis
IQ: Intelligence Quotient
TMT-A: Trail Making Test, task A (Reitan, 1958)

6.5.h. – Suicidal behaviour over the follow-up

Of the 293 FEP cases included in this chapter, 64 subjects (21.8%) made at least one suicide attempt. Thirty-eight individuals (12.9%) had suicidal antecedents prior to first contact with psychiatric services. Eighteen of these subjects (6.1%) also attempted to take their lives over the 7-year follow-up, during which 26 subjects without suicidal antecedents (8.9%) made at least one suicidal act. Eight subjects died from suicide over the 7-year period, which results in an overall case fatality of 2.7% (8/293). Also, 10 more patients died from natural causes, which represents an overall proportionate mortality of 6.1% (18/293) at the end of the follow-up (median=7 years). In terms of attrition, 32 patients (10.9%) could not be traced or they were abroad at the time of suicide-related variables assessment as explained above. Figure 6.1., below, provides a flow chart of suicidal events over the follow-up.

Figure 6.1. GAP-AESOP combined cohort. Flow chart of suicidal events over the study period



GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
FEP: First-episode psychosis

6.5.h.1. – Suicide methods

As shown in figure 6.1. above, over the follow-up 44 subjects attempted to end their lives on at least one occasion and in total there were 80 suicidal events. In terms of methods (see table 6.14., below), poisoning (n=31) and jumping (n=12), which encompasses both jumping off a height and jumping in front of a vehicle, were the most common suicide methods. Also, there were suicide attempts by violent methods such as stabbing (n=3) or fire-setting (n=2). There were no suicide attempts by firearms.

With regard to those subjects who took their lives (n=8), hanging (n=2) and jumping (n=2) were the most common means of suicide. One patient died from taking an overdose, another subject set a fire at home and one patient stabbed himself to death. No specific method was recorded in the remaining (n=16) suicide completers. See Table 6.14, below.

Table 6.14. GAP-AESOP combined cohort: Suicide methods

Method	Events (n=80)
*Poisoning**	26
Cutting superficially	12
*Stabbing**	3
*Jumping**	13
*Hanging**	6
*Setting a fire**	2
Drowning	1
*Unspecified**	1
Unrecorded	16

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
*at least one suicide completion by this mean

6.5.i. – Risk factors for suicidal behaviour over the follow-up

Univariate analyses concerning demographic, clinical and symptom-related variables, including insight, are presented below in tables 6.15, 6.16 and 6.17, respectively.

Table 6.15. GAP-AESOP combined cohort (n=293): Univariate analysis: log-rank tests of equality of survival distributions for the demographic variables

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Gender	Male	24.5	23	0.18	0.67
	Female	17.5	19		
Age at first contact	<28	21.1	26	2.36	0.12
	>28	19.9	15		
Education level	No qualifications	10.2	14	3.79	0.28
	GCSE	10.1	6		
	Higher	13.4	14		
	University	7.3	7		
Living status	**Alone**	**13.7**	**21**	**7.04**	**0.01**
	Not alone	**27.3**	**20**		
Employment status	Unemployed	20.9	17	1.49	0.22
	Employed	20.0	24		
Ethnicity	White	18.0	23	2.38	0.30
	Black	15.4	11		
	Other	7.5	7		

GAP: Genetics and Psychosis Study. AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses

Table 6.16. GAP-AESOP combined cohort (n=293): Univariate analysis: log-rank tests of equality of survival distributions for the clinical and demographic variables

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Previous SA	**Absent**	**36.2**	**26**	**33.11**	**<0.01**
	Present	**5.8**	**16**		
DUP	<48	20.6	21	0.02	0.89
	>48	20.4	20		
Diagnosis	Schizophrenia	28.9	33	2.63	0.27
	Mania	7.1	4		
	Depression	5.9	5		
Alcohol	**non-use**	**6.8**	**2**	**4.38**	**0.04**
	Use	**30.2**	**35**		
Drugs	non-use	15.5	12	1.61	0.20
	Use	26.5	30		
Positive	Absent	8.0	8	0.02	0.89
	Present	30.9	31		
Negative	Absent	18.2	13	3.19	0.07
	Present	20.8	26		
Disorganization	Absent	20.2	24	1.16	0.28
	Present	18.7	15		
Mania	Absent	22.6	27	2.85	0.09
	Present	16.4	12		
Depression	**Absent**	**16.7**	**9**	**8.01**	**<0.01**
	Present	**22.3**	**30**		

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
SA: Suicide attempts (prior to first presentation/contact)

Table 6.17. GAP-AESOP combined cohort: Cox regression analyses for neurocognitive, psychopathological and insight-related variables

Risk factor	RR	95% CI	p-value
Neurocognition			
Full premorbid IQ	0.99	0.97 - 1.02	0.84
Current IQ	0.99	0.99 - 1.00	0.81
TMT-B-A	**1.00**	**1.00 – 1.01**	**0.03**
Insight			
Recognition of illness	1.10	0.99 – 1.23	0.06
Symptoms relabeling	1.08	0.99 - 1.17	0.08
Treatment compliance	**1.35**	**1.10 – 1.64**	**<0.01**
Total insight	**1.06**	**1.01 – 1.11**	**0.01**

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
RR: Relative risk. CI: Confidence Interval.
IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

From the bivariate analyses shown in tables 6.15, 6.16. and 6.17 above, the following factors were found to be associated with time to first suicidal event:, living alone (RR 2.21, 95% CI 1.20-4.08, p=0.01), suicidal history (RR 5.10, 95% CI 2.72-9.56, p<0.01), alcohol use (RR 3.99, 95% CI 0.96-16.58, p=0.06), depression (RR 2.76, 95% CI 1.31-5.82, p=0.01), TMT B-A (RR 1.00, 95% CI 1.00-1.01, p=0.03) and two insight-related variables such as treatment compliance (RR 1.35, 95% CI 1.10-1.64, p<0.01) and total insight score (RR 1.06, 95% CI 1.01-1.11, p=0.01).

As a result, living status, suicidal history, depression, TMT B-A, compliance and total insight were included in a multivariable Cox regression model (enter method) detailed in table 6.18., below. In particular, suicidal antecedents (RR 5.00, 95% CI 2.26-11.04, p<0.01) emerged as the only significant predictor of suicidal behaviour over the follow-up.

Table 6.18. GAP-AESOP combined cohort: Multivariate analysis of risk factors for suicidal behaviour from Cox regression modelling (n=174)

Risk factor		RR	95% CI	p-value
Living status	Alone	2.09	0.84 – 3.84	0.13
	Not alone	1.00		
Previous SA	**Present**	**5.00**	**2.26 – 11.04**	**<0.01**
	Absent	**1.00**		
Depression	Present	1.70	0.69 – 4.17	0.24
	Absent	1.00		
TMT B-A		1.00	0.99 – 1.01	0.09
Compliance		1.19	0.88 – 1.60	0.26
Total insight		1.01	0.94 – 1.08	0.82

GAP: Genetics and Psychosis Study
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses
RR: Relative Risk. CI: Confidence Interval
SA: Suicide attempts (prior to first presentation)
TMT: Trail Making Test (Reitan, 1958)

6.6. – Discussion

6.6.a. – Main findings

In this chapter, I merged two FEP cohorts in order to investigate the relationship between insight levels shortly after first presentation with psychosis and risk of suicidal behaviour over a prolonged follow-up period (median=7 years), which resulted in greater statistical power (over 90%) to detect differences in insight levels equivalent to an effect size of 0.33 with a two-tailed alpha set at 5%.

In the light of the above results, I can draw three conclusions. First, suicidal antecedents prior to first presentation to psychiatric services influence insight levels at that point. Second, depressive symptom severity is related to both suicidal antecedents and insight levels at first presentation. Third, although those subjects who showed suicidal behaviours over the follow-up had higher levels of insight at baseline, these relationships appear to be mediated by other variables such as depression, DUP, and, more importantly, the influence of suicidal history on both insight levels at baseline and future suicidal events.

First, in full agreement with the findings from chapters 4 and 5, as expected, an association of all insight dimensions at first presentation and previous history of suicide attempts was replicated. Unlike chapter 4 and 5, in this cohort such a relationship was also significant for treatment compliance. Moreover, after performing multivariable regression models, previous suicidal history remained an independent significant predictor of total insight score. In addition, further predictors of insight dimensions emerged from the analyses such as DUP (the longer the DUP, the poorer the insight) and gender (females presenting with greater scores on symptoms relabeling) and low education level, which was linked with impaired total insight. Second, in keeping with the above, depressive symptom severity was significantly associated with two insight dimensions: illness recognition and treatment compliance. Interestingly, those patients with suicidal antecedents presented with both higher levels of all insight dimensions and more severe depressive symptomatology.

Third, in contrast to my fifth hypothesis (H5) and chapter 2 (section 2.5), treatment compliance emerged as significant risk factor for suicidal behaviour from the bivariate analyses, although the strength of the association was weak (RR=1.35). However, consistent with my hypothesis H6 (chapter 2, section 2.5), total insight score, although significantly associated with suicidality in the bivariate analyses, did not survive the multivariable regression models, which revealed suicidal history to predict risk of suicidal behaviour over

the follow-up. Further predictors of suicidal behaviour from the bivariate analyses, which did not remain significant in the multivariable regression models, were living status and depression. Hence, it seems that, relatively in line with my hypotheses, SAs prior to first contact, which was also associated with insight levels at that point, behaved as a risk factor for suicidal behaviour over the follow-up. In other words, based on these findings, previous SA may explain, in part, the apparent relationship between insight and future suicide risk in early psychosis, which is consistent with my hypotheses (Chapter 2, section 2.5).

6.6.b. – Suicidal history influences insight levels at first presentation

In keeping with findings from chapters 4 and 5, including a data-based peer-reviewed publication presented in chapter 4, of which I was first author (Lopez-Morinigo et al., 2014a), those subjects with suicidal antecedents were found to have greater insight levels at first presentation than those patients without suicidal history. Of note, unlike chapters 4 and 5, in this chapter the score on treatment compliance was also significantly higher in those subjects with previous suicide attempts than in non-suicide attempters, which was against my expectations. In addition, further predictors of each insight dimension were revealed by the analyses, which would provide further support for the multidimensional model (David, 1990; Amador & David, 2004).

Interestingly, in this chapter (see table 6.9.) I replicated the 'neurocognitive basis of insight in psychosis' (Amador et al., 1991; Morgan & David, 2004; Aleman et al., 2006; Ayesa-Arriola et al., 2011; David et al., 2012; Nair et al., 2014) since I found IQ and some measures of executive function to be associated with all insight dimensions except compliance, which is consistent with previous literature (see Nair et al., 2014 for an up-to-date meta-analysis).

With regard to demographic variables, females, employed people and those of white ethnicity presented with significantly higher insight levels except for compliance. In terms of gender, these findings are in full agreement with previous reports (Wiffen et al., 2012; Parellada et al., 2011; McEvoy et al., 2006) and a meta-analysis (Mintz et al., 2003), although some groups failed to replicate such an association (e.g. Markova, 2005). As alluded to in chapters 4 and 5, white patients had significantly higher levels of insight than those of a Black ethnic origin, consistent with previous literature (Morgan, 2003; Goldberg et al., 2005; Johnson & Orrell, 1995), although a London-based study had reported no differences in insight levels across ethnicities (David et al., 1995). Also, as reported in chapter 4, symptom relabelling and

total insight scores were higher in those with some form of certificated education, i.e. GCSE or higher levels, which is in line with a previous study from our group (Wiffen et al., 2010). In keeping with this, unemployment was linked with poorer insight, although differences in treatment compliance did not reach statistical significance, which was in line with previous, although limited, literature (Lysaker & Bell, 1994).

In line with chapters 3 and 4, I replicated the inverse relationship between insight and DUP (Pek et al., 2006; Saravanan et al., 2010; Cuesta et al., 2011), i.e. the longer the DUP, the poorer the insight at first presentation, which also remained significant in the multivariable regression models for the four insight scores. However, the cross-sectional association did not allow me to draw conclusions in terms of the direction of causality. On the one hand, it can be postulated that lacking insight delays seeking attention and receiving treatment, thus increasing the DUP. On the other hand, it can be argued that a more prolonged DUP results in a more symptomatically severe first presentation, hence with poorer insight (Drake et al., 2000).

Several significant associations of psychopathological symptoms and insight levels were revealed by the analyses. Thus, relabelling was negatively associated with positive symptom severity, in keeping with previous studies (e.g. Mintz et al., 2003; Cuesta et al., 2011), while compliance was linked with negative symptoms, mania and depression. Specifically, those with more severe negative and depressive symptoms were more compliant than those with less severe presentations in those domains. Interestingly, those patients with lower mood scored higher on the compliance item. Of note, depression (rather than psychotic symptoms) showed more significant correlations with insight scores, particularly illness recognition and treatment compliance, which is in full agreement with previous literature (Peralta et al., 1998; Mintz et al., 2003; Cooke et al., 2005; Lincoln et al., 2007; Nair et al., 2014; Belvederi et al., 2015). As detailed in chapter 4 (sections 4.6.c. and 4.6.d.) and chapter 5 (section 4.6.b.), the direction of causality remains unclear, as illustrated by the so-called 'demoralization syndrome' (Drake, 1986; Restifo et al., 2009) and 'depressive realism' (see Ghaemi & Rosenquist, 2004 for a review), respectively.

Of interest to this investigation, it is worth noting that those subjects with suicidal antecedents had more severe depressive symptoms at the time of the assessment, including the evaluation of insight (indeed, those subjects had significantly higher insight levels). Hence, while there is strong evidence to support the existence of a 'depressive-insightful-suicidal'

group of FEP patients, the direction of causality of the above variables requires prospective investigation, which forms the context for the next two sections.

6.6.c. – Insight dimensions and risk of suicidal behaviour over the follow-up

As postulated in chapter 2 (section 2.5., hypotheses H1 and H2), illness awareness and symptom relabeling behaved as risk factors for suicide, although the differences did not reach statistical significance. However, in contrast to my expectations (see hypothesis H5 in chapter 2, section 2.5.), better compliance with treatment was a significant risk factor in the bivariate analyses, as well as total insight score.

In addition, a set of variables were linked with risk of suicidal behaviour from the bivariate analyses, namely living alone, alcohol use, suicidal history, more severe depressive symptoms and a measure of executive functions such as the TMT B-A. These variables were therefore added to a multivariable regression model which revealed suicidal history to predict risk of suicidal behaviour over the follow-up, as explained in section 6.6.d. below.

Hence, these results suggest that insight is not a *direct* risk factor for suicide in early psychosis. Certainly, in the light of my results, it seems that if there was an association of any insight dimension with risk of suicidal behaviours in early psychosis, such an association would be confounded by other variables, namely suicidal history and depression, both of which were significantly associated with insight levels (at baseline) and suicidality over the follow-up. These findings are in line with the seminal paper by Hawton and colleagues (Hawton et al., 2005), which demonstrated insight to be a non-significant risk factor for suicide in schizophrenia, while poor compliance was significantly associated with an increased risk; and a recent meta-analysis of FEP studies (Challis et al., 2013), which reported an overall significant OR of 1.64 (95% CI 1.23-2.56) for insight as risk factor for suicide, but with important exceptions. In particular, treatment compliance was a risk factor in this research, which suggests that being aware of the 'need' for treatment may contribute, to a certain degree, to suicidal behaviour in some, but not all, patients with psychosis from South-East London. The complexity of these relationships is discussed in more detail in chapter 8.

6.6.d. – Predictors of suicidal behaviour over the follow-up

Consistent with chapters 4 and 5, suicidal history emerged as the strongest predictor of future suicidal events, which was in full agreement with previous literature on 'suicide and psychosis' (Hu et al., 1991; De Hert et al., 2001; Sinclair et al., 2004; Hawton et al., 2005; Reutfors et al., 2009; Dutta et al., 2010; Pompili et al., 2011; Björkenstam et al., 2014; Bakst et al., 2010a; Challis et al., 2013; Tarrier et al., 2006), including two recent meta-analyses (Large et al., 2011; Challis et al., 2013). In addition, living alone at baseline, depressive symptom severity and executive functions (as measured by the TMT B-A) were significantly associated with risk of suicidal behaviour over the 7-year follow-up. However, only suicidal history remained significant predictors of suicidal behaviour in the multivariable Cox-regression models, although TMT B-A showed a borderline trend.

In keeping with this, living alone was found to be a significant risk factor for suicidal behaviour, consistent with previous literature (Hawton et al., 2005a; Challis et al., 2013), although this relationship did not survive the multivariable regression models. It should be noted that the living status may have changed over the follow-up, i.e. from the time of the study inception and assessment to the time of the first suicidal event.

As discussed in chapter 5 (section 5.6.d), the relationship between cognitive performance and suicide risk in psychosis remains far from clear (Andersson et al., 2008, Webb et al., 2011; Potkin et al., 2003; Barrett et al., 2011; see Hor & Taylor, 2010 for a general review), although it seems that the stage of the illness may play a relevant part in these conflicting results. In particular, in this sample of FEP patients more impaired executive function, as measured by the TMT B-A, was associated with an increased suicide risk. Although this finding is consistent with previous studies of schizophrenia patients (Fenton et al., 1997; De Hert et al., 2001), the strength of the association (RR=1.01) was too weak for it to be considered as a relevant risk factor for suicide in early psychosis. Hence, further research is warranted in this area, including following cohorts of FEP subjects from first presentation over a prolonged period of time, during which comprehensive cognitive assessments should be carried out.

Of note, in keeping with previous research (e.g. Tsuang, 1978; Osby et al., 2000; Qin & Nordentoft, 2005; Palmer et al., 2005; Limosin et al., 2007; Osborn et al., 2008; Alaräisänen et al., 2009; Dutta et al., 2010; Barrett et al., 2010a; Barrett et al., 2010b), risk of suicidal behaviour was linked with younger age; however, at a non-significant level in this study.

Finally, the link between depression and suicidality was replicated in this FEP sample (Altamura et al., 2003; Hawton et al., 2005; Barrett et al., 2010; Bertelsen et al., 2007; Upthegrove et al., 2010; Flanagan and Compton, 2012; Harvey et al., 2008; Kontaxakis et al., 2004; Barrett et al., 2010a; Barrett et al., 2010b; Pompili et al., 2011), although it did not survive the multivariable regression models. Indeed, as detailed above, depression appears to mediate the potential relationship between insight, particularly treatment compliance, and risk of suicidal behaviours in this FEP cohort.

The results from this chapter are shown in figures 6.2 and 6.3, below, which present the model hypothesised in this investigation (figure 6.2) and the model based on this chapter findings (figure 6.3).

Figure 6.2. Hypothesised model to be tested in this thesis

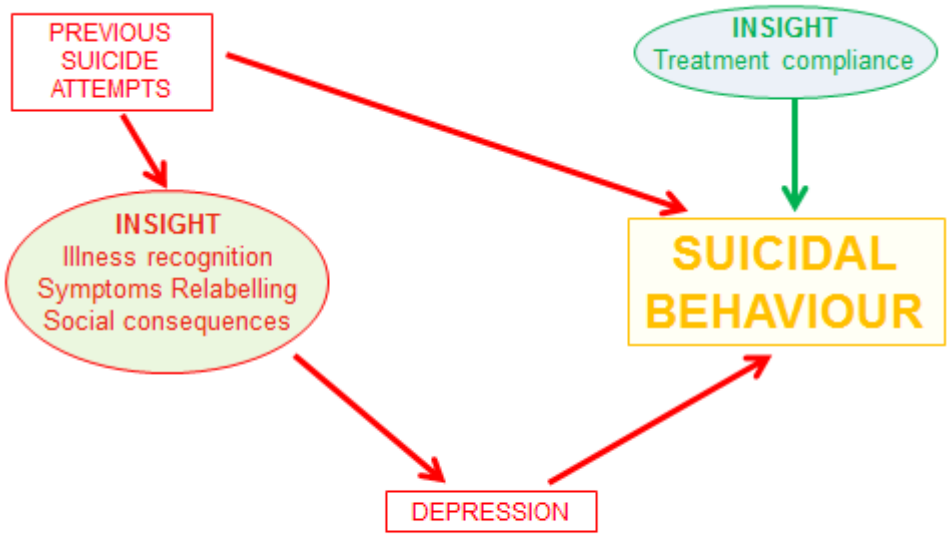
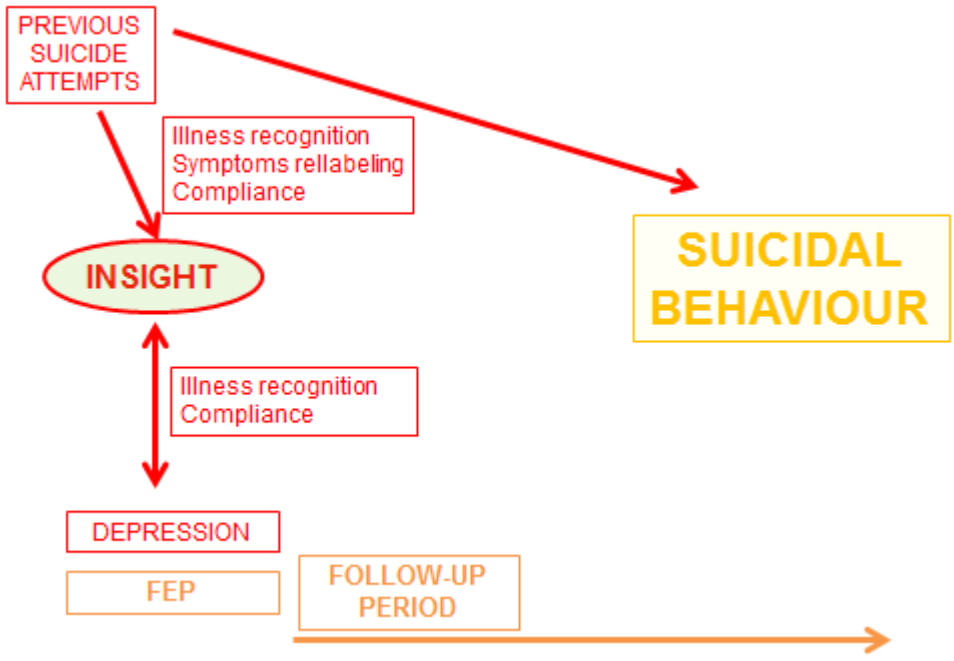


Figure 6.3. Model based on the combined GAP-AESOP cohort results



6.6.e. – Strengths and limitations

The above findings come from a very large cohort of FEP patients who were followed-up over a prolonged period of time (median=7 years). In addition, this cohort comes from two FEP studies which aimed to recruit 'all incident cases' in NHS-funded hospitals from South-East London (the vast majority of participants) and Nottingham, both settings based in the UK. Since most people with psychosis in these two catchment areas receive NHS-funded mental health care, the sample is likely to be representative of the local populations. In addition to the 'sufficient' statistical power, as detailed in section 6.4.c.1., due to using a large sample size and a long follow-up period, a number of variables were comprehensively assessed using validated instruments, including demographic data, clinical antecedents, psychopathological, insight-related and neurocognitive variables.

However, this chapter has several limitations. First, other non-tested variables might affect insight such as premorbid personality (Lysaker et al., 1999; Campos et al., 2011; Cuesta et al., 2011; Ritsner & Blumenkrantz, 2010) and neuroanatomical correlates (Morgan et al., 2010; David et al., 2012). Second, examiners were not blind to other scales such as the PANSS, which might bias the insight assessment (Campos et al., 2011). Third, our cross-sectional assessment of insight did not permit the investigation of insight changes over the course of the illness (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011; Ayesa-Arriola & Lopez-Morinigo et al., 2014) in relation to suicide risk. Also, demographic variables such as living status may have changed over the follow-up period. Moreover, psychopathology and insight have been reported to improve over the early stages of the psychotic illness (e.g. Cuesta et al., 2011; Ayesa-Arriola & Lopez-Morinigo, 2015). Hence, these potential insight changes are likely to have affected suicide risk differently, which requires further studies with several insight assessments over time, which is challenging in the real-world, particularly in terms of reassessing patients with psychosis on a face-to-face basis.

6.7. – Summary of the chapter

In the light of these results, there is no evidence to support a direct association of insight levels with risk of suicidal behaviours in early psychosis, which in this sample was predicted by previous SAs.

With regard to insight, in contrast to my expectations, better treatment compliance emerged as the main insight dimension linked with suicide risk, although all insight dimensions behaved as risk factors in the bivariate analyses. However, depressive symptom severity and suicidal history appeared to confound the above relationships, and this is discussed further in chapter 8.

Chapter 7 – Suicidal behaviour in early psychosis. Findings from a 3-year follow-up first-episode cohort from Santander (Spain)

7.1. – Introduction

This chapter describes the predictors of suicidal behaviour in a 3-year follow-up first-episode psychosis (FEP) study from Santander (Spain). The role of three insight dimensions - namely insight into mental illness (IMI), insight into the social consequences of the illness (ISC) and insight into the need for treatment (INT) - in suicidal behaviours over the follow-up period was investigated. Suicidal behaviours included both suicide attempts (SA) and completions (SC). The analyses were adjusted for demographic and clinical variables, which may mediate or confound the above relationships and therefore influence the rate of suicidal acts.

Parts of the analyses presented in this chapter were published as a peer-reviewed article which I co-authored (Ayesa-Arriola et al., 2015). However, for the purposes of this thesis, I have only considered suicidal events 'after' first presentation with psychosis and I have taken a different statistical approach by conducting Cox regression analyses, thus considering survival to a first suicide attempt over the follow-up in relation to insight levels at baseline. This constitutes a substantial expansion of the content of the aforementioned paper.

7.2. – Background

As explained in chapters 2, chapter 4 (section 4.2.), chapter 5 (section 5.2.) and chapter 6 (section 6.2.), the role of insight dimensions in suicidal behaviour in FEP patients remains unclear (Lopez-Morinigo et al., 2012), which may have crucial clinical implications for suicide prevention in early psychosis.

Although this research question was investigated in chapters 4, 5 and 6 with two cohorts of FEP subjects from two sites in the UK (mainly, London), the statistical power was limited in some of these studies (62.5% in the GAP cohort presented in chapter 4 and 75.1% in the AESOP study, see chapter 5), which may have been resulted in false negative results. Although merging these two FEP cohorts increased the power to 90% (Chapter 6, section 6.4.c.1.), given that the main hypothesis of this thesis was that insight is *not* a direct risk factor for suicide in early psychosis, I also decided to analyse data from a large cohort of FEP patients from a different country (Santander, Spain) in order to compare the findings from both cohorts (UK and Spain), which forms the context for chapter 8 (General Discussion).

7.3. – Aims and Objectives

7.3.a. – Descriptive aims and objectives

- To describe the distribution of insight dimensions according to the outcome of suicidal behaviours, including both suicide attempts and suicide completions.

7.3.b. – Analytical aims and objectives

- To investigate whether there is an association between a history of suicidal behaviours before first presentation with psychosis and insight levels at that point.
- To adjust the above analyses for potential confounders in order to determine independent predictors of insight at baseline, including the role of previous suicidal history.
- To calculate the case fatality of this FEP sample over the 3-year follow-up.
- To identify the risk factors associated with suicidal behaviours in a FEP cohort over a 3-year follow-up.
    - And to determine whether there is an association of insight levels with risk of suicidal behaviours over the 3-year follow-up.
- To test for potential interactions between insight dimensions and other clinical and demographic variables related to risk of suicidal behaviour.
- To formulate a model, based on a multivariable Cox Regression analysis of the above baseline variables, including insight dimensions, for predicting suicidal behaviours over the 3-year follow-up.

7.4. – Method

7.4.a. – Participants, study design and setting

Data for this chapter came from a large epidemiological and 3-year longitudinal study of first-episode psychosis (PAFIP) conducted at the out- and inpatient services of University Hospital Marques de Valdecilla, Santander, Spain. This study was approved by the local institutional review board and informed consent from participants was obtained. A more detailed description of the program has been previously reported (Pelayo-Teran et al., 2008).

Briefly, all referrals to PAFIP over 2001-2010 were screened with the following inclusion criteria: age 15-60 years; living in the catchment area; experiencing their first episode of psychosis; no prior treatment with antipsychotic medication or, if previously treated, a total life time of adequate antipsychotic treatment of less than 6 weeks; meeting DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. DSM-IV criteria for drug dependence and mental retardation and having a history of neurological disease or head injury were exclusion criteria.

Three hundred and ninety seven patients who met inclusion criteria were included in the PAFIP program during this time interval. Diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1996), which was carried out by an experienced psychiatrist 6 months after the baseline visit. The diagnoses (DSM-IV) of participants are presented in table 7.1. below. Two diagnostic categories - 'schizophrenia' and 'other psychoses' - were created for the analyses.

Table 7.1. Santander: Diagnoses of participants

Diagnoses	N (%)
Schizophrenia	224 (56.4)
Schizophreniform disorder	96 (24.2)
Schizoaffective disorder	5 (1.2)
Brief psychotic disorder	41 (10.3)
Psychosis NOS	29 (7.3)
Delusional Disorder	2 (0.5)

NOS: Not otherwise specified

7.4.b. – Measures

7.4.b.1. – Premorbid and sociodemographic variables

Information was obtained from patients, relatives and medical records. This included sex, age at admission, age at illness onset and duration of untreated psychosis (DUP). Other sociodemographic variables collected were: years of education, relationship status ("married/cohabiting" vs. "single/divorced/separate or widowed"), living status ("alone" vs. "other"), socio-economic status derived from the parents' occupation ("low" vs. "other"), employment status ("employed" vs. "unemployed"), living area ("urban" vs. "rural", which included those living in areas with less than 10,000 inhabitants), cannabis and alcohol use (self-reported as yes/no) and first degree family history of psychosis (yes/no). Premorbid social adjustment (PAS) (Cannon-Spoor et al., 1982) and hospitalization (yes/no), and days in hospital where appropriate, were considered.

7.4.b.2. – Baseline clinical and neuropsychological measures

Clinical symptoms of psychosis at study entry were assessed with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983). Global scores were used to generate three symptomatic dimensions: positive, disorganized and negative (Grube et al., 1998). Depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992).

The neuropsychological assessment was carried out when patient clinical status permitted good cooperation, which occurred at a mean of 10.5 weeks after intake. A detailed description of the neuropsychological assessment has been reported elsewhere (Gonzalez-Blanch et al., 2007). Specifically, a measure of overall cognition such as the premorbid IQ, which was estimated by the Wechsler Adult Intelligence Scale III vocabulary test (Lezak, 1995), and executive functioning, which was evaluated with the Trail Making Test (Reitan , 1958), particularly the time to complete task B minus time to complete task A, were considered for the analyses.

7.4.b.3. – Insight assessment

The shortened version of the Scale to Assess Unawareness of Mental Disorder (SUMD) (Amador et al., 1994) was used to measure three insight dimensions: insight into mental illness (IMI), insight into need for treatment (INT), and insight into social consequences of the illness (ISC). 'Poor' insight was defined as SUMD scores greater than 1, and a score of 1 designated 'good insight'. Patients were classified in two groups (good and poor insight). Of note, the SUMD was found to strongly correlate with other insight scales, including the SAI-E (Sanz et al., 1998). Hence, the results were deemed appropriate for cross-comparisons with the findings from the UK cohorts (Chapters 4, 5 and 6), which forms the context for the general discussion (Chapter 8).

7.4.b.4. – Suicide attempts information

Suicidal behaviours, i.e. potentially self-injurious behaviour for which the person intended to kill himself/herself (O'Carroll et al., 1996), were taken from medical records. In particular, any SA before first contact with psychiatric services and any further SAs were registered, which included suicide attempts and suicide completions. Information on suicidal behaviour was available for the entire sample, N=397 patients. SAs methods were dichotomized according to Asberg et al.'s criteria (Asberg et al., 1976) into 'violent' (hanging, jumping from a height, jumping in front of a vehicle, cutting him/herself, setting a fire) and 'non-violent' (i.e. self-poisoning).

7.4.c. – Statistical analysis

The Statistical Package for Social Science version 22.0 (SPSS Inc., Chicago, IL, USA) was used for performing the statistical analyses.

Descriptive analyses and comparison of patient characteristics, including the aforementioned demographic and clinical variables, were undertaken using chi-square, t-tests and Mann-Whitney U tests as appropriate.

First, predictors of insight dimensions at baseline were investigated through binary logistic regression models in order to precisely test the influence of suicidal history on insight levels after adjusting the analyses for potential mediating variables.

Second, all patients were entered into a survival analysis with the end date being the date of first suicide attempt (or suicide completion where appropriate) or the censoring point, i.e. either the date on which the patient was last known to be alive or the end of the 3-year follow-up study period, which commenced at the time of discharge from hospital or after first contact to services in those patients who were not admitted at first presentation.

Risk of suicide over the 3-year follow-up was calculated by considering the proportion of patients who died from suicide of the total initial sample size (i.e. those who were lost to follow-up were included in the denominator), which is known as case-fatality (Palmer et al., 2005).

Survival analyses (Kaplan-Meier Curves and log-rank tests) were performed to compare time from hospital discharge or first appointment for those outpatients who did not require hospitalization to first suicidal event or the censoring point as appropriate across insight groups (good vs. poor insight) for each insight dimension. Participants were censored as non-attempters at the time of the last face-to-face assessment or at 3-year follow-up, whichever came sooner.

In addition, multivariable Mandel-Cox regression models (Cox, 1972) were built up in order to investigate survival in relation to baseline insight variables, whilst adjusting the analyses for potential mediating/confounding demographic and clinical variables.

All of the above analyses were two-tailed and significance level was set at 5%.

7.4.b.6. – Power calculations

Given the variable amount of missing data for each variable, a range of power calculations was performed for suicide risk using the *stpower logrank* command of STATA 11.0 for Windows (StataCorp LP, USA).

Under the assumption of a 20% risk of suicidal behaviour based on previous studies (e.g. Robinson et al., 2010) and given that insight variables, which were dichotomized (see section 7.4.b.3, above) were available on n=352 (i.e. 352/397=88.7%), there was 96.7% power to detect a difference of 2% in risk between groups, which is equivalent with an effect size of 0.5.

7.5. – Results

7.5.a. – Sociodemographic and clinical characteristics of the sample

The sample was comprised of 397 individuals. The sociodemographic and clinical characteristics of the whole sample and differences across patients with/without SA preceding first presentation to services are presented in Table 7.2. below.

Table 7.2. Santander: Sociodemographic and clinical characteristics of the whole sample and differences across patients with/without previous suicide attempts

	Total sample N=397	With previous SA n=25 (6.3%)	Without previous SA n=372 (93.7%)	Statistic	p-value
Gender, males	**226 (56.9%)**	**20 (80%)**	**202 (54.3%)**	**X^2 = 5.87**	**0.01**
Age, years:	29.9 ± 9.5	30.6 ± 9.8	29.8 ± 9.5	t = 0.44	0.66
DUP: days, median	90	75	90	U	0.97
Schizophrenia	224 (56.4%)	18	203	X^2 = 2.60	0.11
Years of education	10.2 ± 3.3	9.9 ± 3.5	10.2 ± 3.3	t = -0.42	0.67
Unmarried	313 (78.8%)	21 (84%)	288 (77.4%)	X^2 = 0.37	0.54
Living alone	57 (14.4%)	2 (8%)	53 (14.2%)	X^2 = 0.82	0.36
Unemployed	176 (44.3%)	14 (56%)	159 (42.7%)	X^2 = 0.15	0.23
Urban area	293 (73.8%)	22 (88%)	267 (71.8%)	X^2 = 2.69	0.10
Cannabis	171 (43.1%)	15 (60%)	153 (41.1%)	X^2 = 3.16	0.07
Alcohol	215 (54.2%)	14 (56%)	198 (53.2%)	X^2 = 0.03	0.86
Family history	88 (22.2%)	2 (8%)	83 (22.3%)	X^2 = 2.72	0.09
Poor Premorbid Adjustment	117 (29.5%)	11 (44%)	106 (28.5%)	X^2 = 2.77	0.09
Premorbid IQ	9.1 ± 2.8	8.8 ± 2.9	9.1 ± 2.8	U	0.55
TMT B-A	62.0 ± 50.4	51.1 ± 38.4	62.7 ± 51.2	U	0.67
SAPS-Positive	13.5 ± 4.3	13.1 ± 4.2	13.5 ± 4.3	U	0.63
SANS-Negative	7.0 ± 6.2	8.2 ± 2.8	7.0 ± 6.1	U	0.77
CDSS	2.3 ± 3.3	3.5 ± 3.6	2.3 ± 3.6	t = 1.74	0.08
Insight Mental Illness	125 (31.5%)	9 (36%)	115 (30.9%)	X^2 = 0.04	0.83
Insight Social Consequences	218 (54.9%)	13 (52%)	202 (54.3%)	X^2 = 0.60	0.44
Insight Need for Treatment	**188 (47.4%)**	**7 (28%)**	**179 (48.1%)**	**X^2 = 6.03**	**0.01**
Hospitalization	**256 (64.5%)**	**23 (92%)**	**227 (61.0%)**	**X^2 = 9.12**	**0.01**
Length of admission (days)	21.5 ± 16.1	28.1 ± 25.6	20.8 ± 14.8	t = 1.35	0.19

SA: Suicide attempts prior to first presentation/contact. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT B-A: Trail Making Test, time to complete task B minus time to complete task A (Reitan, 1958).
SAPS: Scale for the Assessment of Negative Symptoms (Andreasen, 1983) SANS: Scale for the Assessment of Positive Symptoms (Andreasen, 1983). CDSS: Calgary Depression Scale for Schizophrenia (Addington et al., 1992).

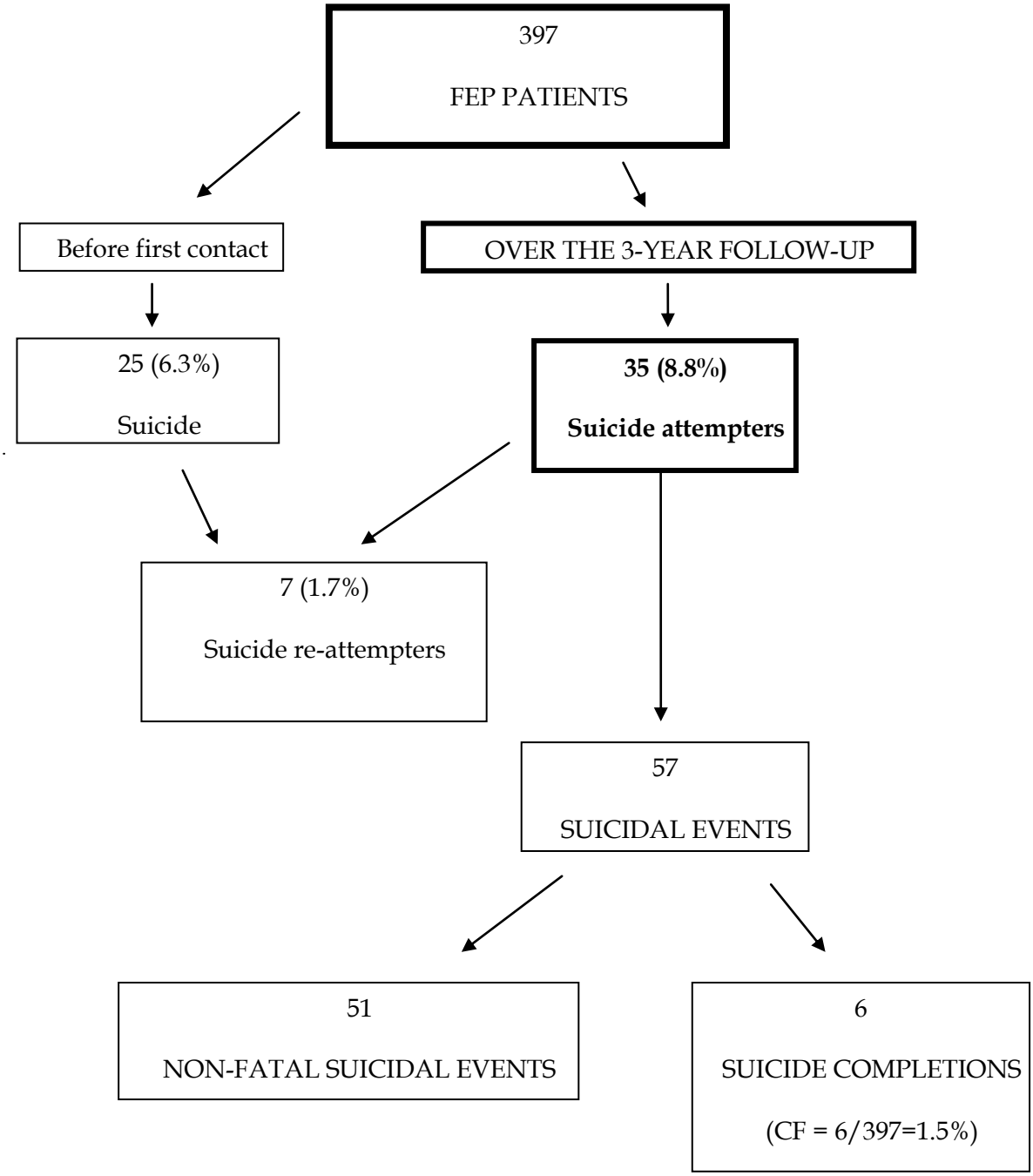
7.5.b. – Suicidal behaviours

Sixty patients (15.1%) made (at least) one suicide attempt. Twenty-five individuals (6.3%) had made a suicidal act before first presentation. Also, 35 subjects (8.8%) attempted suicide on at least one occasion over the 3-year follow-up, including 12 patients (3%) who made two suicide attempts and 5 cases who attempted to take their lives three times after first contact with psychiatric services. Eight patients (2.1%) showed suicidal behaviour both before and after first presentation to services. In addition, 6 subjects (CF=6/397=1.51%) completed suicide over the 3-year follow-up period, which equates to a suicide rate of 603.06 suicides/100,000 persons-year. According to population data from the Instituto Cántabro de Estadística (www.icane.es), the suicide rate in Cantabria in 2010 was 4.48 suicides/100,000 persons-year, which meant the SMR was estimated at approximately 134.6. See Figure 7.1. below.

7.5.b.1. – Suicide methods

Six individuals (25%) took an overdose, while the remaining 19 suicide attempts before first presentation (75%) were categorized as 'violent'. Fifty-seven suicidal events occurred over the follow-up period, with 'non-violent' methods significantly more common (41, 71.9%) than 'violent' suicide attempts (16, 28.1%).

Figure 7.1. Flow chart of suicidal events over the study period



FEP: First-episode psychosis. CF: Case-fatality.

7.5.c. – The influence of previous suicide attempts on insight into having a mental illness

IMI was not found to significantly vary between those patients with and without suicidal acts before first presentation with psychosis, although the proportion of 'suicidal' patients was slightly higher in the 'good IMI' group (7.3%) than in those with poor IMI (6.6%).

However, good insight (when compared with poor insight) was significantly associated with shorter DUP (60 days vs. 120 days, p=0.04), executive functions as evaluated by the TMT B-A (p=0.03), i.e. those with good insight performed better than the poor insight group who took longer to complete the task (53 vs. 66 seconds, respectively, p=0.03), unemployment (36% in good IMI patients vs. 49.8% in poor IMI, p=0.01) and length of hospital admission (16.5 vs. 24.3 days, respectively, p<0.01). The percentage of patients requiring hospitalization did not vary across insight groups. In addition, a diagnosis of schizophrenia (in comparison to 'all other psychoses') was significantly (p=0.01) more common in the poor insight group (62.9%) than in those subjects with good awareness of having a mental illness (46.4%).

Further non-significant differences were revealed in the analyses which are detailed in Table 7.3 below.

Table 7.3. Santander: Comparison of pre-morbid, socio-demographic, clinical and cognitive variables between patients with good and poor insight into having a mental illness

	Good IMI n = 125 (35.5%)		Poor IMI n = 227 (64.5%)			
	n (%)	**Mean ± SD**	**n (%)**	**Mean ± SD**	**Statistic**	**p-value**
Age		30.7 ± 8.9		29.8 ± 10.1	t = 0.90	0.37
DUP (median, days)		**60**		**120**	**U**	**0.04**
Education (years)		10.7 ± 3.5		9.9 ± 3.2	t = 1.89	0.06
Premorbid IQ		9.2 ± 2.7		9.1 ± 2.8	t = 0.15	0.88
TMT B-A		**53.6 ± 39.3**		**66.1 ± 53.5**	**t = - 2.22**	**0.03**
SAPS		13.3 ± 3.9		13.8 ± 4.4	t = - 0.98	0.32
SANS		6.6 ± 5.5		7.2 ± 6.2	t = - 1.54	0.11
CDSS		2.6 ± 3.6		2.1 ± 2.9	t = 1.58	0.11
Length of stay		**16.5 ± 10.7**		**24.3 ± 17.1**	**t = -4.22**	**<0.01**
Gender (males)	69 (56.5)		132 (58.1)		X^2 = 0.29	0.59
Previous SA	9 (7.3)		15 (6.6)		X^2 = 0.04	0.83
Schizophrenia	**58 (46.4)**		**143 (62.9)**		**X^2 = 9.06**	**0.01**
Unmarried	94 (77.0)		188 (82.8)		X^2 = 3.25	0.07
Living alone	13 (10.6)		39 (17.1)		X^2 = 2.99	0.08
Unemployed	**44 (36.0)**		**113 (49.8)**		**X^2 = 7.13**	**0.01**
Urban area	96 (78.7)		165 (72.7)		X^2 = 0.60	0.44
Cannabis	48 (39.3)		103 (45.4)		X^2 = 1.60	0.21
Alcohol	68 (55.7)		124 (54.6)		X^2 = 0.01	0.93
Family history	22 (18.0)		54 (23.8)		X^2 = 1.82	0.18
Poor premorbid adjust.	40 (32.8)		73 (32.1)		X^2 = 0.52	0.47
Hospitalization	75 (61.4)		152 (66.9)		X^2 = 1.70	0.19

IMI: Insight into mental illness. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT B-A: Trail Making Test, time to complete task minus time to complete task A (Reitan, 1958). SAPS: Scale for the Assessment of Negative Symptoms (Andreasen, 1983) SANS: Scale for the Assessment of Positive Symptoms (Andreasen, 1983). CDSS: Calgary Depression Scale for Schizophrenia (Addington et al., 1992). SA: Suicide attempts prior to first contact/presentation

In the light of the above bivariate analyses, DUP, TMT B-A, unemployment, having been diagnosed with schizophrenia (in comparison to 'all other psychoses') and length of hospital admission, which emerged as significant predictors of IMI, were entered into a multivariable binary logistic regression model. Since suicidal history had not been found to be significantly associated with IMI, I did not include this variable in the regression model.

Only length of stay (OR=1.03, 95%CI 1.00-1.06, p=0.02) remained as a significant predictor of IMI (Table 7.4). The model (χ^2=13.49, df=5, p=0.02) explained 9.8% (Nagelkerke R^2) of the variance on IMI and overall classified correctly 65.7% of the cases, particularly 27.9% of 'good IMI' patients and 88.5% of those with 'poor IMI'.

Table 7.4. Santander: Predictors of poor insight into having a mental illness

	B	SE	Wald	p	OR	95% CI
DUP binary	-0.02	0.35	0.01	0.96	0.98	0.49 – 1.96
Unemployment	0.26	0.34	0.58	0.45	1.30	0.66 – 2.53
Schizophrenia	-0.42	0.34	1.55	0.21	0.66	0.34 – 1.27
Hospital stay	**0.03**	**0.01**	**5.18**	**0.02**	**1.03**	**1.00 – 1.06**
TMT B-A	0.01	0.01	1.23	0.27	1.00	1.00 – 1.01

DUP: Duration of untreated psychosis.
TMT B-A: Trail Making Test, time to complete task B minus time to complete task A (Reitan, 1958).

7.5.d. – The influence of suicidal history on insight into the social consequences of the illness

Suicidal history was not significantly associated with ISC (p=0.83), although the proportion of patients with such antecedents was marginally higher in the 'poor insight' group (8.2%) than in the good insight group (6.0%).

However, good insight (when compared with poor insight) was significantly (p<0.01) associated with shorter DUP (60 days vs. 180 days), executive functions as evaluated by the TMT B, i.e. those with good insight performed better than the poor insight group who took longer to complete the task (53.8 vs. 69.9 seconds, respectively), years of education (10.5 vs. 9.7, p=0.04), negative symptoms severity as measured by the SANS (6.2 vs. 7.8, p=0.02), depressive severity evaluated by the CDSS scores (2.6 vs. 1.7, respectively, p=0.01), poor premorbid adjustment (p=0.01) and length of hospital admission (17.9 vs. 27.1 days, respectively, p<0.01), although the percentage of patients requiring hospitalization did not vary across insight groups. Again, the percentage of patients diagnosed with schizophrenia was significantly (p<0.01) greater in the poor insight group (75.4%) than in those with good ISC (45.9%).

Further non-significant differences are shown in Table 7.5.

Table 7.5. Santander: Comparison of pre-morbid, socio-demographic, clinical and cognitive variables between patients with good and poor insight into the social consequences of the illness

	Good ISC n = 218 (61.9%)		Poor ISC n = 134 (38.1%)			
	n (%)	**Mean ± SD**	**n (%)**	**Mean ± SD**	**Statistic**	**p-value**
Age		30.1 ± 8.9		30.1 ± 10.8	t = 0.05	0.96
DUP (median)		**60**		**180**	**U**	**<0.01**
Education (years)		**10.5 ± 3.3**		**9.7 ± 3.3**	**t = 2.10**	**0.04**
Premorbid IQ		9.3 ± 2.6		8.7 ± 2.9	t = 1.62	0.10
TMT B-A		**53.8 ± 45.3**		**69.9 ± 54.3**	**t = - 2.03**	**0.04**
SAPS		13.3 ± 3.9		14.1 ± 4.7	t = - 1.65	0.10
SANS		**6.2 ± 5.7**		**7.8 ± 6.3**	**t = - 2.31**	**0.02**
CDSS		**2.6 ± 3.4**		**1.7 ± 2.8**	**t = 2.79**	**0.01**
Length of stay		**17.9 ± 12.1**		**27.1 ± 18.6**	**t = -4.11**	**<0.01**
Gender (males)	121 (55.5)		80 (59.7)		$X^2 = 0.60$	0.44
Previous SA	13 (6.0)		11 (8.2)		$X^2 = 0.60$	0.44
Schizophrenia	**100 (45.9)**		**101 (75.4)**		**$X^2 = 29.49$**	**<0.01**
Unmarried	168 (77.0)		114 (85.0)		$X^2 = 3.07$	0.08
Living alone	26 (11.9)		26 (19.4)		$X^2 = 3.62$	0.06
Unemployed	89 (40.8)		68 (50.7)		$X^2 = 3.17$	0.07
Urban area	167 (76.6)		94 (70.1)		$X^2 = 2.01$	0.16
Cannabis	93 (42.7)		58 (43.2)		$X^2 = 0.01$	0.91
Alcohol	121 (55.5)		71 (52.9)		$X^2 = 0.26$	0.61
Family history	48 (22.0)		28 (20.9)		$X^2 = 0.06$	0.80
Poor premorbid adjust.	**59 (27.0)**		**54 (40.3)**		**$X^2 = 10.86$**	**<0.01**
Hospitalization	134 (61.4)		93 (69.4)		$X^2 = 2.28$	0.13

ISC: Insight the social consequences. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT B-A: Trail Making Test, time to complete task minus time to complete task A (Reitan, 1958). SAPS: Scale for the Assessment of Negative Symptoms (Andreasen, 1983) SANS: Scale for the Assessment of Positive Symptoms (Andreasen, 1983). CDSS: Calgary Depression Scale for Schizophrenia (Addington et al., 1992). SA: Suicide attempts prior to first presentation/contact.

DUP, years of education, a diagnosis of schizophrenia, TMT B-A, SANSS, CDSS, premorbid adjustment and length of hospital admission, which emerged as significant predictors of ISC from the bivariate analyses, were entered into a multivariable binary logistic regression model. Since suicidal history had not been found to be significantly associated with IMI, this variable was not added to the model.

Only a diagnosis of schizophrenia (OR=0.38, 95% CI 0.17-0.84, p=0.02) and severity of depressive symptomatology as measured by the CDSS (OR=0.790, 95% CI 0.671-0.93, p<0.01) predicted 'poor' ISC (Table 7.6). The model (χ^2=38.50, df=8, p<0.01) explained 27.7% (Nagelkerke R^2) of the variance on ISC and overall classified correctly 72.7% of the cases, namely 85.8% of 'good insight' patients and 47.5% of the 'poor insight' subjects.

Table 7.6. Santander: Predictors of poor insight into the social consequences of the illness

	B	SE	Wald	p	OR	95% CI
DUP binary	-0.56	0.38	2.09	0.15	1.75	0.82 – 3.71
Education (y)	-0.01	0.06	0.03	0.87	0.99	0.89 – 1.11
Schizophrenia	**-0.96**	**0.40**	**5.72**	**0.02**	**0.38**	**0.17 – 0.84**
Days in hospital	0.02	0.01	2.83	0.09	1.06	1.00 – 1.06
TMT B-A	0.01	0.00	0.72	0.40	1.06	1.00 – 1.06
Premorbid ad.	0.34	0.39	0.75	0.39	1.40	0.65 – 3.03
SANS	0.05	0.03	2.56	0.11	1.05	0.99 – 1.12
CDSS	**-0.23**	**0.08**	**8.19**	**<0.01**	**0.79**	**0.67 – 0.93**

DUP: Duration of untreated psychosis. TMT B-A: Trail Making Test, time to complete task minus time to complete task A (Reitan, 1958). SANS: Scale for the Assessment of Positive Symptoms (Andreasen, 1983). CDSS: Calgary Depression Scale for Schizophrenia (Addington et al., 1992). Premorbid ad: Poor premorbid adjustment

7.5.e. – The influence of suicidal history on insight into the need for treatment

Those individuals with 'good' insight were less likely to have made suicidal acts before first contact with mental health services than 'poor' insight patients as follows: 3.7% vs. 10.3%, p=0.01.

However, good insight (when compared with poor insight) was significantly associated with shorter DUP (67.5 days vs. 150 days, p=0.02), years of education (10.6 vs. 9.7, p=0.01), positive symptoms severity as measured by the SAPS (13.1 vs. 14.2, p=0.01), depressive severity which was assessed by the CDSS scores (2.7 vs. 1.8, respectively, p=0.02), unemployment (39.9% vs. 50.0%, p=0.05), poor premorbid adjustment (p=0.01) and length of hospital admission (16.9 vs. 26.4 days, respectively, p<0.01), although the percentage of patients requiring hospitalization did not vary across insight groups. There were significantly (p=0.01) more patients with schizophrenia who had poor INT (64%) than subjects with this diagnosis and good INT (51.1%).

Further non-significant differences were found which are shown in Table 7.7.

Table 7.7. Santander: Comparison of pre-morbid, socio-demographic, clinical and cognitive variables between patients with good and poor insight into the need for treatment

	Good INT n = 188 (53.4%)		Poor INT n = 164 (46.6%)			
	n (%)	**Mean ± SD**	**n (%)**	**Mean ± SD**	**Statistic**	**p-value**
Age		30.8 ± 9.4		29.3 ± 9.8	t = 1.54	0.12
DUP (median)		**67.5**		**150**	**U**	**0.02**
Education (years)		**10.6 ± 3.4**		**9.7 ± 3.2**	**t = 2.49**	**0.01**
Premorbid IQ		9.4 ± 2.7		8.9 ± 2.7	t = 1.45	0.15
TMT B-A		57.8 ± 45.3		65.9 ± 53.0	t = - 1.37	0.17
SAPS		**13.1 ± 3.8**		**14.2 ± 4.7**	**t = - 2.47**	**0.01**
SANS		6.5 ± 5.8		7.2 ± 6.3	t = - 1.05	0.30
CDSS		**2.7 ± 3.4**		**1.8 ± 2.9**	**t = 2.40**	**0.02**
Length of stay		**16.9 ± 10.3**		**26.4 ± 18.4**	**t = -4.83**	**<0.01**
Gender (males)	105 (55.8)		96 (58.5)		X^2 = 0.26	0.61
Previous SA	**7 (3.7)**		**17 (10.3)**		**X^2 = 6.03**	**0.01**
Schizophrenia	**96 (51.1)**		**105 (64.0)**		**X^2 = 6.01**	**0.01**
Unmarried	145 (77.1)		137 (83.5)		X^2 = 2.65	0.10
Living alone	28 (14.9)		24 (14.6)		X^2 = 0.01	0.96
Unemployed	**75 (39.9)**		**82 (50.0)**		**X^2 = 3.83**	**0.05**
Urban area	146 (77.6)		115 (70.1)		X^2 = 2.31	0.12
Cannabis	75 (39.9)		76 (46.3)		X^2 = 1.49	0.22
Alcohol	102 (54.2)		90 (54.9)		X^2 = 0.01	0.95
Family history	42 (22.3)		34 (20.7)		X^2 = 0.13	0.71
Poor premorbid adjust.	**52 (27.6)**		**61 (37.2)**		**X^2 = 6.60**	**0.01**
Hospitalization	134 (71.3)		93 (56.7)		X^2 = 2.28	0.13

INT: Insight the need for treatment. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT B-A: Trail Making test, time to complete task minus time to complete task A (Reitan, 1958). SAPS: Scale for the Assessment of Negative Symptoms (Andreasen, 1983) SANS: Scale for the Assessment of Positive Symptoms (Andreasen, 1983). CDSS: Calgary Depression Scale for Schizophrenia (Calgary et al., 1992). SA: Suicide attempts prior to first presentation/contact.

DUP, years of education, a diagnosis of schizophrenia, SAPSS, CDSS, suicidal history, unemployment, poor premorbid adjustment and length of hospital admission, which emerged as significant predictors of insight into the need for treatment from the bivariate analyses, were entered into a multivariable binary logistic regression model.

Only suicidal history (OR=3.72, 95% CI 1.17-11.80, p=0.02), length of stay (OR=1.04, 95% CI 1.01-1.07, p=0.01) and depressive severity as evaluated by the CDSS total score (OR=0.86, 95% CI 0.77-0.96, p=0.01), which showed an inverse relationship (i.e. 'poor' insight was linked to more severe depressive symptomatology) remained as independent significant predictors of INT (Table 7.8). The model (χ^2=38.10, df=9, p<0.01) explained 23.5% (Nagelkerke R^2) of the variance on INT and overall classified correctly 66.5% of the cases. Specifically, 69% of 'good insight' patients and 63.9% of the 'poor insight' subjects were correctly identified by the model.

Table 7.8. Santander: Predictors of poor insight into the need for treatment

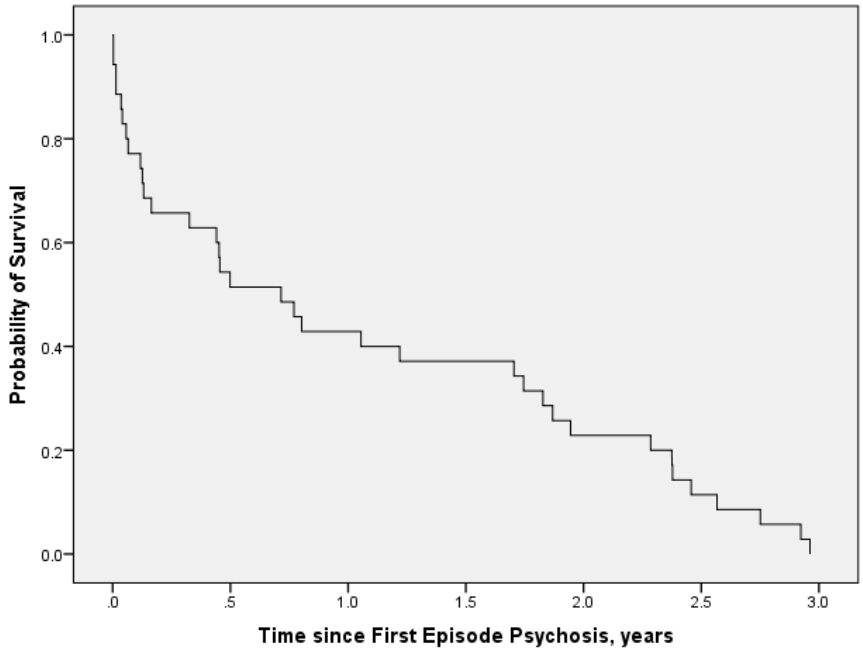
	B	SE	Wald	p	OR	95% CI
DUP (binary)	-0.41	0.35	1.40	0.23	1.51	0.76 – 3.01
Education (y)	-0.08	0.05	2.30	0.08	0.92	0.83 – 1.01
Schizophrenia	-0.10	0.34	0.01	0.76	0.90	0.46 – 1.76
Previous SA	**1.31**	**0.59**	**4.99**	**0.02**	**3.72**	**1.17 – 11.80**
Days in hospital	**0.04**	**0.01**	**6.69**	**0.01**	**1.04**	**1.01 – 1.07**
Unemployment	-0.32	0.34	0.90	0.34	0.72	0.37 – 1.41
Premorbid ad.	0.30	0.35	0.76	0.38	1.35	0.69 – 2.67
SAPS	0.05	0.04	1.56	0.21	1.06	0.97 – 1.15
CDSS	**-0.15**	**0.06**	**6.92**	**0.01**	**0.86**	**0.77 – 0.96**

DUP: Duration of untreated psychosis. TMT B-A: Trail Making Test, time to complete task minus time to complete task A (Reitan, 1958). SAPS: Scale for the Assessment of Positive Symptoms (Andreasen, 1983). CDSS: Calgary Depression Scale for Schizophrenia (Addington et al., 1992). SA: Suicide attempts prior to first presentation/contact

7.5.f. – Risk factors for suicidal behaviour over the 3-year follow-up

As detailed in section 7.5.b., 35 follow-up suicide attempters, including 6 suicide completers, and 362 non-suicide attempters were compared through Kaplan-Meier survival analyses and Cox Regression models with regard to baseline insight levels, whilst adjusting the analyses for demographic and clinical mediating/confounding variables. The first suicide attempt was more likely to occur within the first year (20/35=57%) than in the remaining two years (15/35=43%), which was statistically significant ($p<0.01$). Specifically, the first suicide attempt (n=35) occurred within a median follow-up time of 261 days, as shown by the Kaplan-Meier Curve below (Figure 7.2.).

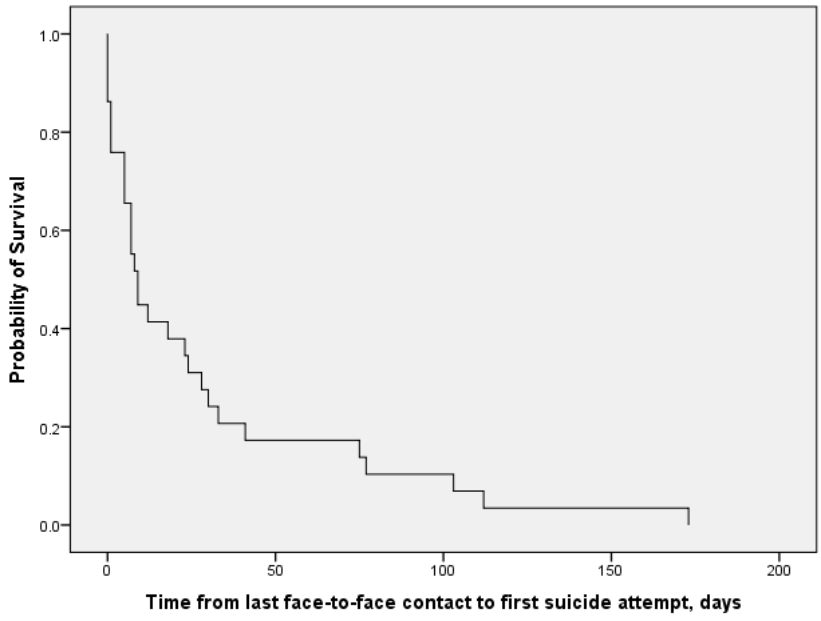
Figure 7.2. Santander: Kaplan-Meier Survival Curve showing time to first suicidal event over the follow-up in suicide attempters and completers, n=35 (Median: 0.71 years, 95% CI: 0.31-1.12)



In total, there were 57 suicidal events over the 3-year follow-up, including 6 suicide completions. 35 attempters made just one suicidal act over the follow-up, 11 individuals made two suicide attempts over the 3-year follow-up and 5 patients attempted to take their life on 3 occasions over the 3-year follow-up.

The date of the last face-to-face review before the 57 suicidal events over the 3-year follow-up was recorded in 45 cases (78.9%). The median for this time was 9 days for the first suicide attempt, 23 days for the second suicide attempt and 3 days for the third suicidal act. 15 suicidal events occurred within the first week after a face-to-face contact with a PAFIP member of the staff. Figure 7.3. below shows the Kaplan-Meier Survival Curves for time from last face-to-face contact to first suicide attempt (n=35):

Figure 7.3. Santander: Kaplan-Meier Survival Curve showing time (days) from last face-to-face contact to first suicidal event over the follow-up in suicide attempters and completers, n=35 (Median: 9.00 days, 95% CI: 5.50-12.50)



With regard to suicide method, poisoning (n=23) and cutting (n=13) were the most common suicide methods. Also, there were suicide attempts by violent methods such as hanging (n=3) and jumping (n=5), which included jumping from a height or in front of a train. There were no suicide attempts by firearms.

In terms of attrition, the 362 non-suicide attempters were censored at a mean follow-up time of 1095 days. Only 63 non-suicidal subjects (63/362=17.4%) did not complete the 3-year follow-up.

Univariate analyses concerning demographic, clinical and symptom-related variables, including insight, are presented below in tables 7.9, 7.10 and 7.11, respectively.

Table 7.9. Santander: Survival analyses of demographic variables

Risk factor		**Events expected**	**Events observed**	**Log-rank test (X^2)**	**p-value**
Gender	Male	19.9	22	0.72	0.40
	Female	15.1	13		
Age	<27.7	17.2	22	2.85	0.09
	>27.7	17.7	13		
Years of education	<10	19.3	22	1.37	0.24
	>10	15.6	13		
Unmarried	Unmarried	27.7	29	0.26	0.61
	Married	7.3	6		
Living alone	Alone	5.2	4	0.29	0.59
	Not alone	29.9	31		
Urban area	Urban area	25.9	28	0.86	0.35
	Rural area	9.1	7		

Table 7.10. Santander: Univariate analysis: log-rank tests of equality of survival distributions for the clinical variables

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Suicidal history	**Absent**	**35.7**	**22**	**16.33**	**<0.01**
	Present	**2.2**	**7**		
DUP	<90	17.9	15	0.61	0.43
	>90	17.0	19		
Schizophrenia	Absent	15.2	13	0.59	0.44
	Present	19.7	22		
Cannabis	Absent	19.9	19	0.33	0.56
	Present	15.1	16		
Alcohol	Absent	9.7	9	0.56	0.75
	Present	5.8	12		
Family history psychosis	**Absent**	**26.4**	**22**	**4.04**	**0.04**
	Present	**7.5**	**12**		
Hospitalization	Absent	12.4	10	0.81	0.37
	Present	22.5	25		
Length of stay, days	<18	13.1	15	0.52	0.43
	>18	11.9	10		

DUP: Duration of untreated psychosis

Table 7.11. Santander: Univariate analysis: log-rank tests of equality of survival distributions for the neuropsychological and symptom-related variables

Risk factor		Events expected	Events observed	Log-rank test (X^2)	p-value
Premorbid adjustment	**Good**	**16.8**	**11**	**5.81**	**0.02**
	Poor	**9.2**	**15**		
Premorbid IQ	Low	10.3	14	3.34	0.07
	High	8.7	5		
Executive functions	Preserved	5.2	5	0.04	0.85
	Impaired	15.8	16		
Positive symptoms	Absent	17.5	17	0.02	0.88
	Present	17.4	18		
Negative symptoms	Absent	18.4	17	0.32	0.57
	Present	16.6	18		
Depression	**Absent**	**29.6**	**23**	**11.91**	**0.01**
	Present	**4.4**	**11**		
Insight mental illness	Absent	16.7	17	0.07	0.79
	Present	9.2	9		
Insight social consequences	Absent	9.9	9	0.04	0.84
	Present	16.1	17		
Insight need for treatment	Absent	12.1	12	0.02	0.96
	Present	13.9	14		

Young age (<27.7 years, which was the median) at first presentation (RR 1.79, 95% CI 0.90-3.55, p=0.09), suicidal history (RR 4.87, 95% CI 2.08-11.4, p=0.02), family history of psychosis (RR 2.03, 95% CI 1.00-4.09, p=0.05), poor premorbid adjustment (RR 2.52, 95% CI 1.16-5.48, p=0.02), and depression (RR 3.30, 95% CI 1.61-6.76, p<0.01) were most strongly related to risk of suicidal behaviour.

No insight dimension was significantly associated with risk of suicidal behaviour over the follow-up.

Most of suicidal acts occurred shortly after the last appointment with a PAFIP member of the staff. The median of this time was 18 days for the first attempts (n=35), 22 days for the second attempt (n=12) and 3 days for the third attempt (n=3). However, 16 suicidal events (35.5%) were made over a month after the last appointment.

Young age at first presentation (<27.7 years), suicidal history, family history of psychosis, poor premorbid adjustment and depression were entered into the first forward stepwise Cox regression model. Age at first contact (RR 2.61, 95% CI 1.07-6.32, p=0.03), suicidal history (RR 4.35, 95% CI 1.50-12.62, p<0.01), poor premorbid adjustment (RR 2.34, 95% CI 1.00-5.45, p=0.05) and depression (RR 4.39, 95% CI 1.91-10.10, p<0.01) remained significant as shown in table 7.12. below.

Table 7.12. Santander: Multivariate analysis: Risk factors for suicidal behaviour from Cox regression modelling – sociodemographic, clinical and symptom-related variables

Risk factor		RR	95% CI	p-value
Age at first presentation	**<27.7**	**2.61**	**1.07 – 6.32**	**0.03**
	>27.7			
Suicidal history	**Present**	**4.35**	**1.50 – 12.62**	**<0.01**
	Absent			
Family history psychosis	Present	0.47	0.19 – 1.17	0.11
	Absent			
Poor premorbid adjustment	**Present**	**2.34**	**1.00 – 5.45**	**0.04**
	Absent			
Depression	**Present**	**4.39**	**1.91 - 10.10**	**<0.01**
	Absent			

Model based on n=326 first episode psychosis cases (including 24 suicide attempters) which had complete data for all the variables in the model.

7.6. – Discussion

7.6.a. – Main findings

Four main findings emerged from the analyses, which provide support for my hypotheses.

First, in a cohort of all patients presenting with a first-episode of psychosis in the Cantabria catchment area over 2001-2010 and followed-up over 3 years, I identified a high number of patients who attempted to end their lives over that period, including six people who died by suicide. When compared with the general population of Cantabria, I also found this cohort to have a significantly higher risk of suicide completion, thus reflecting the importance of suicide prevention in early psychosis. Moreover, the use of violent methods was relatively common despite the non-fatal outcome in most cases.

Second, no relationships between suicidal history and insight dimensions at first presentation were revealed by the analyses except for INT. Specifically, those patients who lacked INT at first presentation were more likely to have a suicidal history before first contact with psychiatric services than those subjects with good INT; hence suggesting that awareness of the need for treatment may reduce suicide risk in early psychosis.

Third, no insight dimensions at baseline were associated with an increased risk of suicidal behaviours over the 3-year follow-up despite having sufficient statistical power (96.7%) to investigate these relationships.

Fourth, poor premorbid adjustment, previous SAs, depression and young age at first contact with services were the main risk factors in those individuals who were more likely to make suicide attempts over the 3-year follow-up.

7.6.b. – Epidemiology and suicide methods in the sample

Despite the commonly quoted figure of a "10%" lifetime suicide risk in schizophrenia based on previous research (Miles, 1977; Caldwell & Gottesman, 1990), I replicated the more recently findings from FEP cohorts (Bertelsen et al., 2007; Robinson et al., 2010; Dutta el al., 2010), which reported a case-fatality between 1.3-1.9% (1.5% in this FEP sample from Santander).

In keeping with the seminal meta-analysis by Brown (1997), I found a very significant increased suicide risk in the first three years of the psychotic illness in this cohort in comparison with the general population of this catchment area (Cantabria, Spain); thus replicating previous studies that reported suicide to be the largest single cause of death in psychotic disorders (Brown et al., 1997; Dutta et al., 2010). It remains unclear, however, what is the rate of suicide in people with undiagnosed psychosis (Nielssen & Large, 2009). It should be noted that almost half of suicide attempters prior to first presentation to services made suicidal acts before the onset of psychosis as rated by the DUP, which is consistent with recent research showing that having psychotic experiences predicts future suicidality in adolescents at a population level (Kelleher et al., 2013) and in clinical samples (Kelleher et al., 2014).

In addition, given the non-fatal outcome of most of suicide attempts, taking an overdose was the most common suicide method, which was in line with previous samples of suicide attempters with schizophrenia spectrum disorders (Altamura et al., 2003; Baca-Garcia et al., 2005) and FEP (Fedyszyn et al., 2011). In spite of the non-fatal outcome in most cases, a number of attempters used violent methods such as jumping in front of a vehicle or from a high place, in line with previous reports (e.g. Nielssen et al., 2010; Lopez-Morinigo et al., 2014b). However, patients with schizophrenia and related disorders were reported to kill themselves by taking overdoses in Finland (Heilä et al., 1997). Of note, no suicide attempts by firearms were identified in our study, which is in line with previous reports from Europe (e.g. De Hert et al., 2001; Dutta et al., 2010), reflecting the legal restrictions to access firearms compared to the USA.

7.6.c. – Previous suicide attempts and insight dimensions at first presentation

In spite of previous findings from our group (Lopez-Morinigo et al., 2014a) and other FEP studies (e.g. Barrett et al., 2010a) suggesting that previous suicidal events before first presentation with psychosis may affect insight levels at that point, I failed to replicate these associations in this cohort from Santander (Spain) except for INT. Although these negative results may have been due to insufficient statistical power, this seems to be very unlikely. An alternative explanation is that most of these suicidal events occurred shortly before first contact with services (within the previous month) and therefore, they cannot be considered to be, in reality, 'previous' suicide attempts (i.e. they actually occurred during the 'acute' phase of the illness).

With regard to IMI, it should be noted that the proportion of 'good IMI' patients was, however, slightly higher in the suicidal group. A negative relationship between insight and DUP was replicated (Pek et al., 2006; Cuesta et al., 2011; Saravanan et al., 2010; Lopez-Morinigo et al., 2014a), i.e. the longer the DUP, the poorer the insight at first presentation. However, the direction of causality remains unclear since it is at least as likely that poor insight leads to avoidance of care and hence increases DUP (Drake et al., 2000). Similar findings were found with regard to ISC and INT in relation to DUP in the bivariate analyses, although these associations did not survive the multivariable regression models. Moreover, the risk of suicidal events over the follow-up was lower in those with a short DUP (<90 days). Hence, it seems that shortening DUP, for instance through early detection programmes, may improve insight and reduce suicide risk in patients with schizophrenia spectrum disorders (Altamura et al., 2003; Nielssen & Large, 2009; Chan et al., 2014). However, a randomised controlled trial from Denmark, which compared patients with a FEP receiving an 'integrated treatment' with those subjects under 'treatment as usual' over a 5-year follow-up, failed to demonstrate that such a specific intervention on early psychosis reduced suicidality (Bertelsen et al., 2008).

In addition, impaired frontal lobe functions were linked with poor IMI in this cohort, which was consistent with previous literature (Ayesa-Arriola et al., 2010; Wiffen et al., 2012; David et al., 2012). However, cognition does not seem to determine long-term insight (Ayesa-Arriola & Morinigo, 2014). Also, unemployment and a diagnosis of schizophrenia were found to be associated with lack of IMI, which was also linked to length of hospital stay, i.e. the poorer the insight, the longer the admission. Although only length of stay survived the multivariable regression models, no causality conclusions can be drawn from these cross-

sectional analyses. Also, for those patients requiring hospitalization, it should be noted that insight was assessed over the admission period.

Although it is intuitive to think that being aware of the social consequences of the illness such as becoming unemployed or partnership breakup may lead to feelings of hopelessness, including suicidal ideation, I did not find suicidal history to be associated with insight into the social consequences of the illness (ISC) at first presentation. However, the multivariable regression analyses found ISC to be determined by having schizophrenia (as opposed to 'other psychoses') and depression at baseline, which was consistent with previous research (Amador et al., 1994; Ayesa-Arriola et al., 2011; Ayesa-Arriola & Morinigo, 2014). Of note, those patients with suicidal antecedents presented with more severe depression at baseline.

A problem here is recall bias - where patients are relied upon to give previous instances of suicide attempts. Thus, a more insightful patient may be more likely to remember and report such events, which of course are likely to be distressing, and they may also be more readily recalled if the current mood state is low (Harvey et al., 2008; Gonzalez, 2008; Schennach-Wolff et al., 2009). Also, on the basis of so-called depressive realism (Ghaemi & Rosenquist, 2004), I may postulate that depressive patients tend to think more pessimistically, thus being more likely to recall true negative events such as having a mental illness, which may result in higher insight scores. This source of bias does not only represent a challenge to researchers in determining the true association between insight and suicidality but also highlights the need for more theoretical discussion about the direction of causality between insight and 'depression' (Beck et al., 1990; Belvederi-Murri et al., 2015).

Finally, INT was found to be related to suicidal history. Those individuals with good INT at baseline were less likely to have suicidal antecedents than those subjects unaware of the need for treatment. In keeping with this, DUP was found to be significantly shorter in patients with good insight, including the three insight dimensions evaluated in this cohort: IMI, ISC and INT. Hence, insight, particularly INT, may reduce suicide risk in early psychosis by leading the individual to seeking psychiatric attention earlier and via shortening DUP and subsequently, decreasing the likelihood of suicidal events before first presentation, which is also the strongest predictor of future suicidal acts in schizophrenia (Hawton et al., 2005) and FEP (Pompili et al., 2011). In keeping with this, the multivariable regression models revealed that length of stay and depression were the only predictors of INT at baseline. Hence, depression seems to be linked with INT, although this cross-sectional association does not

allow me to infer causality conclusions. Regardless of the direction of causality, this 'insightful-depressive' subgroup of FEP patients appeared to have a lower suicide risk before first presentation with psychosis in this cohort. However, this finding should be taken cautiously since in this cohort suicidal 'history' included only very recent suicidal events (within the last month). Indeed, in the London FEP sample this 'insightful-depressive' subgroup of patients was found to be at higher risk of suicidal behaviours before first contact with services, including lifetime suicidal events (Lopez-Morinigo et al., 2014a; Chapter 4). Nonetheless, our results were in line with previous FEP studies (Barrett et al., 2010b), which also showed that insight, as measured unidimensionally through the PANNS (Kay et al., 1987) item, was associated with suicidality independently of negative beliefs about psychosis and depression (Barrett et al., 2010b). However, no causality conclusions can be drawn from these two cross-sectional studies (Barrett et al., 2010b; Lopez-Morinigo et al., 2014a), which forms the context for the next section focused on the relationship between insight levels at baseline and suicidality over the 3-year follow-up.

7.6.d. – Insight dimensions did not increase risk of suicidal behaviours

In line with the specific hypotheses of this PhD (Chapter 2, section 2.5) concerning the role of insight in suicidal behaviours in early psychosis, the results presented in this chapter suggest that insight dimensions at baseline did not seem to predict risk of suicidal behaviours in this FEP cohort over a 3-year follow-up, consistently with the findings from the UK-based cohorts (Chapters 4, 5 and 6). Although it could be argued that these relationships were not found due to insufficient statistical power, there was 97.6% power to test for these associations, as detailed in section 7.4.b.6. Hence, this explanation appears to be unlikely. As a result, I may conclude that, indeed, insight does not behave as a risk factor for suicidal behaviours in early psychosis despite common assertions to the contrary, which deserves further discussion below.

In Chapter 2 I summarized the findings from my MEDLINE-based systematic review concerning studies related to 'insight and suicide risk in schizophrenia' (Lopez-Morinigo et al., 2012). In particular, 5 (Bakst et al., 2009; Bourgeois et al., 2004; Acosta et al., 2009; Robinson et al., 2010; Yen et al., 2002) out of the 7 follow-up selected studies (Bakst et al., 2009; Bourgeois et al., 2004; Acosta et al., 2009; Robinson et al., 2010; Yen et al., 2002; Robinson et al., 2009, Crumlish et al., 2005) failed to find such an association. Therefore, the negative results presented in this chapter appear to be in full agreement with the findings from this systematic review (Lopez-Morinigo et al., 2012), which have been replicated more recently (Fedyszyn et

al., 2011). Moreover, a recent 1-year follow-up FEP study suggests that the relationship between insight and suicide risk may change over the course of the illness. Thus, insight at baseline was found to be associated with increased risk of suicidality at 1-year, whilst the gain of insight over the 1-year follow up reduced the risk at that point (Barrett et al., 2015).

In addition, I demonstrated that those studies reporting a positive association between IMI and suicide risk, particularly those with a cross-sectional design, appear to be subject to both selection and recall bias (Lopez-Morinigo et al., 2012).

Hence, a direct link between insight and suicide in psychosis remains unproven but may be mediated by other variables such as depression, which is consistent with the results from this cohort concerning the role of depression in risk of suicidal behaviours. A correlation between level of insight and depression has been consistently demonstrated (Belvederi et al., 2015), although some inconsistencies were reported in adolescents with early-onset FEP (Parellada et al., 2011). Specifically, this recent meta-analysis reported a significant association of awareness of mental illness and awareness of social consequences with depression, while no such relationship was replicated between depression and compliance (Belvederi et al., 2015). However, the direction of causality remains poorly understood and both directions can be currently supported. First, some insight dimensions (i.e. awareness of the social consequences of the illness) may lead the patient with a psychotic disorder to a more depressive state (Amador et al., 1996), which has been called the 'demoralization syndrome' (Drake et al., 1985; Drake & Cotton, 1986; Amador et al., 1996; Restifo et al., 2009). And second, the so-called 'depressive realism model' may provide the pathway through which a more depressed patient would tend to confront difficult issues such as illness, disability and so on (Ghaemi & Rosenquist, 2004). Thus, this hypothetically more depressed patient would express higher levels of insight. There is thus a 'chicken and egg' dilemma here that can only be solved with longitudinal intervention studies; for example, if it was shown that insight improving interventions reduced suicidality. Certainly, there is no evidence that insight improving interventions worsen suicidality (Pijnenborg et al., 2013).

In contrast to our expectations based on the aforementioned meta-analysis (Belvederi et al., 2015), which linked ISC with depression, I failed to replicate this association in this cohort. Although this negative result may be attributed to limited statistical power, the power calculations presented in section 7.4.c.1 suggest that this is unlikely. However, a genuine smaller effect cannot be excluded. An alternative explanation is the focus of PAFIP on meeting patient's social needs from first contact. For instance, all PAFIP patients are encouraged and

supported to enroll vocational courses in order to get employed. Also, almost half of participants were living in rural areas, where social cohesion may minimize the impact of potentially unmet social needs on suicidality, consistently with the Durkheim's sociological theories of suicide (Durkheim, 1897).

Interestingly, half of the suicidal events over the follow-up occurred shortly after (within 9 days) the last face-to-face contact with a member of the staff, which is in keeping with previous studies showing the relative inability of clinicians to predict, and prevent, imminent suicide risk in individuals with SSD under their care (Hu et al., 1991; Heilä et al., 1997; Tarrier et al., 2006; Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016).

7.6.e. – Predictors of suicidal behaviour over the follow-up

The bivariate analyses revealed that young age at first presentation (<27.7 years), suicidal history, family history of psychosis, poor premorbid adjustment and depression were related to risk of suicidal behaviours over the follow-up. Also, poor premorbid adjustment, previous SAs, depression and age at first presentation survived the multivariable regression models.

Thus, I replicated an increased risk in early stages of the psychotic illness as measured by age at first contact (e.g. Tsuang, 1978; Osby et al., 2000; Qin & Nordentoft, 2005; Palmer et al., 2005; Limosin et al., 2007; Osborn et al., 2008; Alaräisänen et al., 2009; Dutta et al., 2010; Barrett et al., 2010a; Barrett et al., 2010b), although a large nation-wide population-based study from Finland reported late first contact (>30 years) to reduce suicide risk (Hëila et al., 1997). In keeping with this, late illness onset reduced suicide risk in an epidemiological study from Taiwan (Kuo et al., 2005). Nevertheless, close monitoring in early psychosis has been strongly recommended by recently reviewed guidelines (Popovic et al., 2014; NCISH, 2015), which is in line with real-world data from the South London and Maudsley NHS Foundation Trust case register (Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016; Chapter 3). Moreover, findings from our London cohort (Lopez-Morinigo et al., 2014a) suggest that a number of suicidal events occur even before the onset of psychosis as rated by the DUP. It could be therefore speculated that a number of very young individuals with undiagnosed psychosis end their lives before first presentation to psychiatric services (Nielssen & Large, 2009; Andriopoulos et al., 2011). Prospective studies are required for this, including cohort studies which follow individuals from a point prior to their first illness presentation; for instance, by recruiting participants from the so-called 'at-high-risk' or 'prodromal' services.

Regarding gender, although I replicated an association of being male with risk of suicide (Hawton et al., 2005; Limosin et al., 2007; Hor and Taylor, 2010; Dutta et al., 2011; Pompili et al., 2011), the differences did not reach significance, which was in line with previous similar case-control studies with samples of both schizophrenia (Reutfors et al., 2009) and FEP (Björkenstam et al., 2014) patients. Moreover, some of these studies revealed similar suicidal risk across genders (Large et al., 2011) or even a greater risk for females (Thorup et al., 2007).

Also, I found no association of level of education with suicide risk despite previous positive studies in both schizophrenia (e.g. Reutfors et al., 2009) and FEP (Björkenstam et al., 2014). Furthermore, education level was linked with insight levels in patients with

schizophrenia and related disorders in a previous report from our group (Wiffen et al., 2010), i.e. the higher the education level, the greater the insight.

In terms of area of residence, no differences emerged from the analyses between living in rural or urban areas. However, it has been reported that living in rural areas increases the risk of suicide due the availability of firearms and more limited access to mental healthcare (Searles et al., 2013), which is consistent with another study that found lower levels of urbanicity to be associated with higher risk of suicide by firearms (Burros et al., 2013). However, living in urban areas was also linked with an increased suicide risk by jumping. Hence, urbanicity, as opposed to living in rural areas, may have different associations with suicide risk across countries. Specifically, I may speculate that living in rural areas in Cantabria behaved as a protective factor due to increased social cohesion, which is, to some extent, related to the Durkheim's sociological theories of suicide (Durkheim et al., 1897).

Interestingly, the risk of suicidal events over the follow-up was lower in those with a short duration of untreated psychosis (DUP) (<90 days), although this difference did not reach significance. Hence, it seems that shortening DUP, for instance through early detection programmes, may reduce suicide risk in patients with schizophrenia spectrum disorders (Altamura et al., 2003; Barrett et al., 2010a).

I replicated the role of suicidal history in future suicidal events in early psychosis (Hu et al., 1991; De Hert et al., 2001; Sinclair et al., 2004; Hawton et al., 2005; Reutfors et al., 2009; Dutta et al., 2010; Björkenstam et al., 2014; Bakst et al., 2010a; Challis et al., 2013; Tarrier et al., 2006), including a recent meta-analysis (Large et al., 2011). Specifically, 6.3% of our FEP attempters over the 3-year follow-up had made suicide attempts prior to the study inception, which was also a predictor of future suicide attempts in the bivariate analyses, consistently with previous research (eg. Hawton et al., 2005; Pompili et al., 2011). These results were therefore consistent with previous FEP studies (e.g. Robinson et al., 2009, Harvey et al., 2008), including the UK-based cohorts used in this investigation (Lopez-Morinigo et al., 2014a; Chapters 4, 5 and 6). Although most of these 'previous' suicidal acts occurred within the month before first presentation and therefore further suicidal events may have happened at earlier stages, it should be noted that up to 42% of patients with schizophrenia spectrum disorders who end their own lives have no suicidal history (Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016).

Of note, my findings concerning the relationship between having a family history of psychosis and risk of suicide were in line with a recent national register-based cohort study with FEP patients admitted in Sweden (Björkenstam et al., 2014).

In addition, I replicated the high risk of suicide during the immediate period after hospitalization (Hu et al., 1991; Sinclair et al., 2004; Heilä et al., 1997; De Hert et al., 2001; Alaräisänen et al., 2009; NCISH, 2015). Half of suicides occurred in the 6-month period after being discharged from a psychiatric ward. Hence, close monitoring over that period of time should be strongly recommended (Popovic et al., 2014; NCISH, 2015). Moreover, this study showed that the highest self-harm rates occurred shortly before and after psychiatric hospitalization, which is in full agreement with a literature review about suicide risk factors in FEP (Pompili et al., 2011). Therefore, earlier intervention, including hospitalization as appropriate, appears to be needed to better manage the high risk of suicide in the prodromal stages of psychosis. Also, a high level of support should be provided on discharge from hospital, although recent findings from the 2015 UK national Confidential Inquiry into Suicide and Homicide suggest that Crisis and Resolution Home Treatment Teams do not seem to safely manage the high risk of suicide over that period, which is of particular concern for those patients who live alone (NCISH, 2015).

Of note, while in the past inpatient suicides in schizophrenia were relatively common (Caldwell et al., 1990; Heilä et al., 1997), in today's psychiatry hospital appears to provide a safe environment to patients (NCISH, 2015). On the other hand, a high level of support is required to safely manage FEP patients who have been recently discharged from hospital (Popovic et al., 2014; NCISH, 2015). In this regard, it remains unclear the extent to which Crisis and Resolution Home Treatment Teams (NCISH, 2015) and early intervention services (Bertelsen et al., 2007; Castle & Singh, 2015) may reduce suicide risk in patients recently discharged from hospital after a first episode of psychosis.

In contrast to previous literature, neither alcohol (Potkin et al., 2003; Limosin et al., 2007) nor drugs (Hawton et al., 2005; Limosin et al., 2007) were associated with an increased risk of suicidal behaviours in this FEP sample.

The relationship between cognition and suicide risk remains unclear. Thus, three previous large nation-wide studies (Andersson et al., 2008, Webb et al., 2011) found high IQ to be a risk factor for suicide in schizophrenia, while in the general population high IQ reduces this risk (Andersson et al., 2008). The results concerning the lack of association between premorbid IQ and suicide risk over the 3-year follow-up in this FEP cohort were consistent

with some (Potkin et al., 2003; Barrett et al., 2011), but not all, previous studies in this area (see Hor & Taylor, 2010 for a general review). However, cognitive decline may prevent patients with schizophrenia and related disorders from dying by suicide (Fenton et al., 1997; De Hert et al., 2001). Thus, further research is warranted to clarify whether or not cognitive impairment may prevent patients with schizophrenia and related disorders from suicide. In particular, it seems that while cognitive impairment may behave as risk factor in early psychosis, those patients with poorer cognitive performance in later stages of the illness may have a lower suicide risk. Hence, FEP cohorts should be followed-up over a long period of time to investigate this matter. More recently (Martinez-Aran & Vieta, 2015), it has been suggested that cognitive reserve and cognitive enhancement may mediate the relationships between cognition and clinical outcomes, including suicide, which deserves future research. However, poor premorbid adjustment identified suicide attempters independently of other variables, which was consistent with a previous systematic review (Hor & Taylor, 2010).

Interestingly, I found no associations of psychotic symptom severity with suicide risk. Previous studies have yielded mixed results. In particular, replication studies conducted in the 90s (Fenton et al., 1997; Fenton, 2000) reported negative symptoms to prevent suicide in patients with schizophrenia spectrum disorders. In addition, these reports (Fenton et al., 1997; Fenton, 2000) found suicide completers to present with more severe positive symptoms than those who did not take their lives. It should be noted, however, that participants in these studies were long-term inpatients who were discharged from hospital between 1950 and 1975. Hence, these patients were not treated with atypical antipsychotics, which have been reported to reduce suicide risk in schizophrenia (Reutfors et al., 2013), particularly clozapine (Meltzer et al., 2003; Bourgeois et al., 2004). On the other hand, positive symptoms, particularly hallucinations, may reduce suicide risk in schizophrenia (Hawton et al., 2005).

The role of depression in suicidality was replicated in this FEP cohort, which is consistent with previous literature (Altamura et al., 2003; Hawton et al., 2005; Barrett et al., 2010; Bertelsen et al., 2007; Flanagan and Compton, 2012; Harvey et al., 2008; Kontaxakis et al., 2004; Barrett et al., 2010a; Barrett et al., 2010b; Pompili et al., 2011).

In my literature review summarised in chapter 2 (Lopez-Morinigo et al., 2012), three 'negative' selected studies (i.e. they failed to link insight with suicidality) did find depression to be a significant risk factor for suicide, even after adjusting the analyses for potential confounders (Bakst et al., 2009; Barrett et al., 2010; Restifo et al., 2009). More precisely, hopelessness behaved as the strongest predictive factor for suicidality among patients with

schizophrenia in three selected studies (Kim et al., 2003; Bourgeois et al., 2004; Acosta et al., 2009), consistent with Hawton et al's findings (Hawton et al., 2005). This symptom, rather than depression *per se*, may therefore represent the main clinical target for the management of patients with schizophrenia spectrum disorders to reduce the risk of them developing a suicidal behaviour (Pompili et al., 2004).

Hence, while hopelessness appears to be one of the main risk factors for suicide in early psychosis, the case register-based case-control study with suicide completers with schizophrenia presented in chapter 3 showed that hopelessness was relatively uncommon amongst those who ended their lives. In other words, the impact of hopelessness, and probably depression in a broad sense, appears to be more relevant in early stages of the illness, consistent with the previous literature (Pompili et al., 2011; Ayesa-Arriola et al., 2015).

However, it remains unclear whether 'depression' in early psychosis represents a symptomatic domain in its own right (Peralta et al., 2013) or a psychological consequence of the social consequences of the psychotic illness onset (Drake & Cotton, 1986). Thus, a recent 12-month follow-up first-episode psychosis study found that while malevolent voices, use of safety behaviour and subordination to persecutors were associated with depression in the acute FEP, post-psychotic depression was linked to loss, shame, low level continuing positive symptoms and longer duration of untreated psychosis (Upthegrove et al.,2014). In line with the results from this Santander cohort, a previous first episode study from our group found an association between suicidal behaviour preceding first contact with services and depression at that point (Lopez-Morinigo et al., 2014a; Chapter 4), which was also replicated by the study presented in chapter 5. Also, depression in the prodromal stage was reported to predict both suicidality at first presentation and further depressive episodes both in the acute and recovery stages of FEP (Upthegrove et al., 2010). This association seems to challenge, to some extent, the so-called demoralization syndrome (Drake and Cotton, 1986) since depression in early psychosis appears to behave as a trait-like phenomenon (Upthegrove et al., 2010) rather than a psychological reaction to the social consequences of such a devastating illness. Overall, depression seems to play a crucial role in suicide risk in schizophrenia (Hawton et al., 2005) and FEP (Pompili et al., 2011). However, there is little guideline in the management of depression in schizophrenia and related disorders (Siris, 2000; NICE, 2015).

One clinically relevant aspect to mention concerns the difficulties that clinicians so frequently find in distinguishing negative and depressive symptoms (Siris, 2000; Siris, 2001). In terms of suicidality, this distinction may play a crucial role. While depression in schizophrenia

behaves as a risk factor for suicide, the presence of negative symptoms may make this fatal outcome much less likely (Fenton et al., 1997), which may have resulted in depressive symptoms in psychotic patients being undertreated, or even untreated (Addington et al., 2002).

A recent meta-analysis (Belvederi et al., 2015) reported insight, particularly IMI and ISC, to be significantly associated with depression. Interestingly, this meta-analysis (Belvederi et al., 2015) failed to link compliance with depression, on which I had based my hypothesis H5, i.e. compliance as a protective factor for suicidality. Although no insight dimension was associated with an increased risk of suicidal behaviours over the follow-up, I found that those patients with good insight into the need for treatment were less likely to have suicidal background before first presentation. Hence, based on this finding I may hypothesize that awareness of the need for treatment reduces suicide risk in (very) early psychosis. Thus, the lack of associations of baseline INT with suicidal behaviours over the follow-up may be due to insight changes over time (Saeedi et al., 2007; Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011; Ayesa-Arriola et al., 2015). In other words, I speculate that those non-suicide attempters over the follow-up may have greater levels of INT at a later point rather than at baseline, which was not evaluated by this study. Indeed, this is consistent with a recent 12-month follow-up first-episode study from Norway (Barrett et al., 2015), which demonstrated that those subjects who gained insight (which was measured by the PANSS (Kay et al., 1987) item) over the follow-up had lower levels of suicidality at that point, which was assessed by the item 8 of the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992).

In summary, while depression at first presentation predicted risk of suicidal behaviours over the follow-up, as expected, and depression was linked with two insight dimensions at that point, namely ISC and INT, no insight dimension was associated with an increased risk of suicidal behaviours over the 3-year follow-up. In other words, it seems that although insight may lead to an immediate state of low mood or depression, including increased suicidality, consistent with the so-called demoralization syndrome (Drake & Cotton, 1986) or the 'insight paradox' (Lysaker et al., 2007), in the longer-term these insightful patients may present with better mood and reduced suicide risk (Pijnenborg et al., 2013). Thus, figure 7.4, below, shows the model tested in this thesis, while figure 7.5 integrates the findings from this chapter.

Figure 7.4. Hypothesised model to be tested in this thesis

Red arrows increase risk and green arrows reduce risk

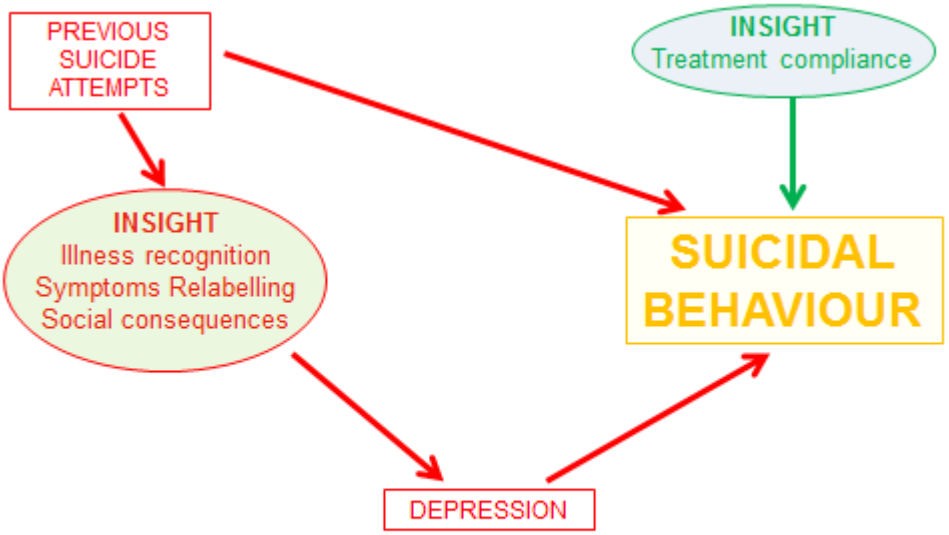
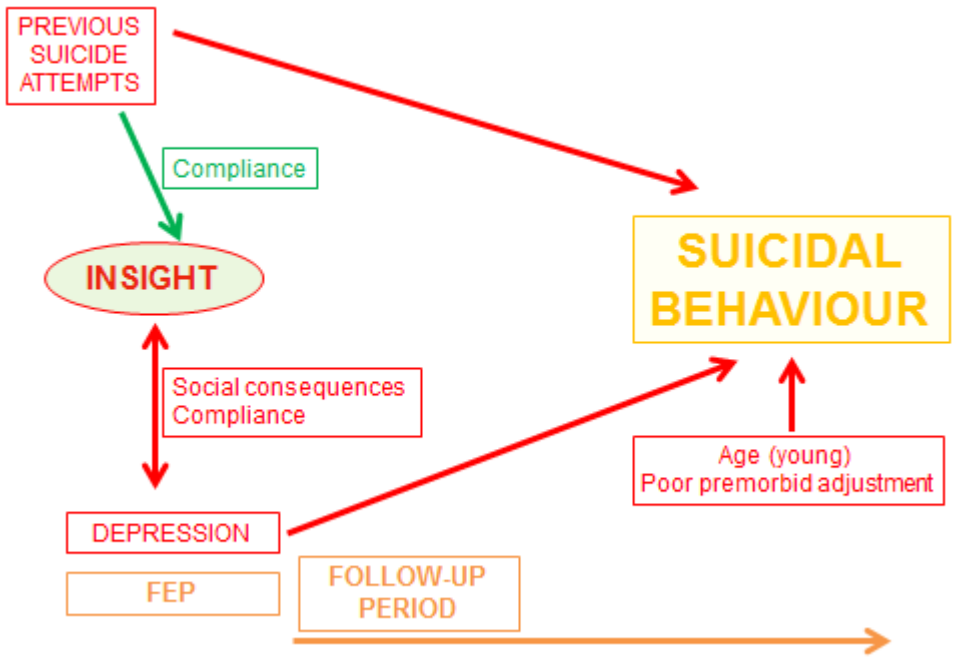


Figure 7.5. Model based on the Santander cohort results

Red arrows increase risk and green arrows reduce risk



7.6.f. – Strengths and weaknesses

Of note, I included a relatively large sample (n=397) of FEP patients who were followed-up over a 3-year period. This allowed sufficient statistical power (from 71.1% to 84.4% depending on the amount of missing data for each variable) to investigate between-groups differences. Moreover, our sample included both in- and outpatients from urban and rural areas, which was therefore very likely representative of the catchment area population (Cantabria, Spain). In addition, a wide range of potential contributing variables was analyzed through Cox-Mandel regression models, thus taking into account the effect of time on variables, i.e. survival.

However, several study limitations should be borne in mind when interpreting the results. First, follow-up information on suicidal behaviour was taken retrospectively from the medical records, which might have resulted in underestimating suicide attempts. In addition, some FEP patients may have completed suicide before contacting psychiatric services, thus also increasing the risk of underestimation. Second, a lack of sufficient statistical power to test for certain interactions cannot be excluded, although this seems to be unlikely based on the power calculations. Third, other non-tested variables may contribute to suicide risk in FEP. Fourth, several variables were dichotomized due to little variability of scores across patients, which may have increased the risk of false positives. Finally, 'baseline' predictors, including insight variables, may have changed over the follow-up period and therefore their associations with suicide risk should be taken cautiously, particularly regarding late stages of the follow-up period.

7.7. – Summary of the chapter

In summary, our results suggest that young age at first presentation with psychosis, suicidal history, family history of psychosis, poor premorbid adjustment and depression are useful markers to identify those patients with a first episode psychosis at higher risk of suicide. Of note, no insight dimensions at baseline, including IMI, ISC and INT, were linked with increased suicide risk over the 3-year follow-up period. Therefore, depression seems to emerge as the main therapeutic target to reduce suicide risk in early psychosis.

Chapter 8 – General Discussion

8.1. – Summary of thesis findings

The main aim of this thesis was to investigate the role of three insight dimensions in risk of suicidal behaviour in early psychosis. First, I provided some general background to the topic (Chapter 1), including an up-to-date systematic literature review (Chapter 2), which was also peer-reviewed and later published (Lopez-Morinigo et al., 2012). Then, I provided real-world data on suicide by patients with schizophrenia and related disorders from the South London and Maudsley NHS Foundation Trust (SLaM) (Chapter 3), which also resulted in two peer-reviewed publications of which I was first author (Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016). Finally, I analysed comprehensive data pertaining to my research question from three cohorts of patients with a first-episode psychosis (FEP), which was presented in Chapters 4, 5, 6 and 7. This chapter therefore aims to summarise and integrate all the above findings, including a reflection on their clinical implications, the methodological strengths and limitations and some suggestions for future research.

8.2. – Literature review

As detailed in chapter 2, I conducted a systematic review of previous studies, by using three major databases namely MEDLINE, PsychInfo and EMBASE, which looked at the association of insight with risk of suicidal behaviour in samples of patients with schizophrenia and related disorders. Twenty studies met the predetermined selection criteria. A meta-analysis could not be conducted due to significant methodological differences between the studies, such as the insight assessment tool, participants' illness stage, study design (cross-sectional vs. prospective) and the lack of consistent quantitative data required for meta-analysis.

In contrast to the commonly held view among clinicians, fourteen out of the twenty selected studies failed to find a *direct* association between insight into having a mental illness and an increased risk of suicidal behaviour, which was also consistent with my first hypothesis H1 (see chapter 2, section 2.5, for further details).

In addition, I postulated up to four reasons underlying the above mixed results, namely selection and recall bias, to which cross-sectional studies are particularly subject, the scale used

to assess insight (unidimensional vs. multidimensional) and the extent to which other contributory factors such as depression-related variables had been taken into account. This led me to formulating the hypotheses listed in chapter 2 (section 2.5), i.e. the confounding role of depression in the relationship between insight dimensions and suicidality, and it also provided me with additional information on the methodological aspects to be considered when conducting my own research (Chapters 4, 5, 6 and 7).

8.3. – Suicide by patients with schizophrenia under secondary mental healthcare

In chapter 3 I used a large database from the South London and Maudsley NHS Foundation Trust (SLaM), which is known as the Case Records Interactive Search (CRIS) (Stewart et al., 2009; Perera et al., 2016). Thus, of 242,227 SLaM service users until 31st December 2013, 635 suicides were identified, which included 96 subjects with a primary diagnosis of schizophrenia spectrum disorder (SSD) (F2-ICD10) who took their lives, although 25 individuals were removed from the analyses due to poor quality of data as they had died prior to 2007, leaving a sample of n=71 patients with SSD who ended their lives.

Hence, nearly one in five of the suicide completers had a diagnosis of psychosis, which was almost double that in a previous meta-analysis of psychological autopsy studies (Cavanagh et al., 2003; Arsenault-Lapierre et al., 2004). While this finding probably reflects the high prevalence of psychotic disorders in South-East London (Fearon et al., 2006), it may also highlight the importance of suicide prevention in patients with psychosis residing in our catchment area, which supports further the need for this investigation (Chapters 4-7).

In particular, by using the above sample of suicide completers with SSD I conducted two case-control studies (see chapter 3 for further details). First, I compared those suicide completers with SSD with those suicide completers with all other diagnoses and I found that most of the classic suicide risk factors (for instance, suicidal ideation/plans, hopelessness, impulsivity and significant loss) were more common in the non-SSD group (Lopez-Morinigo et al., 2014b). Disengagement, which links with impaired insight in psychosis (Amador & David, 2004), was more frequent in the SSD patients, although the difference (p=0.06) was not statistically significant (Lopez-Morinigo et al., 2014b).

The above results led me to speculating that the classic suicide risk assessment model may be of little relevance for patients with SSD (Lopez-Morinigo et al., 2014b). In order to test this hypothesis I compared the above suicide completers with SSD with a control group of

patients with SSD under SLaM teams who did not end their lives. This work resulted in a peer-reviewed publication, of which I am first author (Lopez-Morinigo et al., 2016).

Although older age at first contact with mental health services and lack of both suicidal history and suicidal ideation emerged as useful protective markers, the overall performance of the model, which was based on widely recognized risk assessment factors, was very poor, with a very low positive predictive value of 6%, although the negative predictive value was 96% (Lopez-Morinigo et al., 2016). This discouraging finding was, however, in full agreement with recent literature reporting on the limited positive predictive value of suicide risk assessment scales irrespective of diagnosis (Quinlivan et al., 2016) and the NICE guidelines, which no longer recommend risk assessment tools (NICE, 2011). Moreover, concerns have been voiced about the futility of risk assessment in schizophrenia (Large & Ryan, 2014), which is consistent with my observational finding that most SSD patients who took their lives did so shortly after (even within a few days of) their last face-to-face contact with a staff member. One may think that these suicidal patients were engaged with the teams, which may therefore lead to speculation that insight, which is related to engagement, increases suicide risk. However, no insight assessment was recorded in this study, which was based on data from a large case register, and therefore, such a conclusion cannot be drawn from these results. Also, I postulate that attending the appointment is not conceptually the same as having insight; for instance, many patients with schizophrenia who lack insight do attend their appointments due to legal restrictions (i.e. the UK Community Treatment Order, DoH (2008)), or just as part of a routine or in order to address social needs (for example, benefits or housing issues), yet they deny having a mental illness.

Also, it is noteworthy that insight was not part of the above risk assessment and therefore, these data, while providing further support for the importance of suicide research in schizophrenia and related disorders, did not allow me to answer my main research question. However, a history of disengagement was more common (although at a non-significant level, $p=0.33$) in the suicide completers group than in controls (i.e. those patients with SSD who did not take their lives), thus suggesting that insight may prevent SSD from suicide via better engagement.

8.4. – Previous suicide attempts affect insight levels at first presentation

It should be noted that the two UK-based FEP cohorts included in this investigation (from the GAP and AESOP studies) found illness recognition and total insight to be affected by SA prior to first presentation to services. This adds a relevant confounder to my research project since previous suicide attempts are the strongest predictor of future suicidal acts both in schizophrenia (Hawton et al., 2005) and FEP patients (Challis et al., 2013). Consistent with this, the Santander-based study (Chapter 7), which did not include an overall measure of insight, revealed treatment compliance to be associated with suicidal history and this relationship also survived the multivariable regression models. However, it is noteworthy that those FEP patients with suicidal antecedents were more likely to have poor insight into the need for treatment, which suggests that these patients have a tendency to try and deal with problems themselves. Also, the FEP studies presented in Chapters 4-7 reported other variables such as DUP, cognitive deficits and depression to contribute to insight at first presentation, thus mediating the relationships between suicidal history and insight levels at that point, which did not survive the multivariable models except treatment compliance in the Santander-based study. Table 8.1. below provides a summary of the studies' findings regarding the influence of suicidal history on insight dimensions at first presentation (bivariate analyses).

Table 8.1. Previous suicide attempts and insight dimensions in FEP

	GAP	AESOP	GAP-AESOP	SANTANDER
Recognition	+	+	+	-
Relabelling	+	-	+	n/a
Compliance	-	-	+	+
Social consequences	n/a	n/a	n/a	-
Total insight	+	+	+	n/a

GAP: Genetics and Psychosis Study (Chapter 4)
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses (Chapter 5)
+: There was a significant association. -: There was no significant association. n/a: Not applicable

8.5. – The role of insight in suicidal behaviour in early psychosis

With regard to the role of insight at baseline in predicting suicidal behaviour over the follow-up, contrary to my expectations, the study presented in chapter 4, which was based on data from the GAP study, found awareness of the need for treatment to be associated with an increased suicide risk over the 3-year follow-up study period, while total insight showed a borderline relationship. However, no insight score survived the multivariable Cox-regression models, which was relatively in line with my postulations, particularly regarding the role of mediating/confounding variables such as suicidal history and depression in the relationship between insight dimensions and suicide risk.

In keeping with this, chapter 5 (AESOP data-based) reported no associations of insight scores with risk of suicidal behaviour over the 10-year follow-up, although illness recognition, treatment compliance and total insight showed some trends (p-value<0.1 but >0.05). Hence, these results may suggest that insight behaves as a risk factor for suicide, which may have not been detected by the analyses owing to insufficient power (75%). In order to increase this power, I decided to merge both GAP and AESOP FEP cohorts, as shown in chapter 6, reaching over 90% power to detect an effect size of 0.33 in differences across groups on the SAI-E, which is considered to be clinically meaningful (Kemp & David, 1997). Yet, no significant relationships between insight levels and risk of suicidal behaviour over the follow-up (median=7 years) emerged from the analyses, which was also in full agreement with the negative findings from the Santander cohort (chapter 7), with n=397 subjects followed-up over 3 years and 97% power.

Hence, the principal finding from this research work, which is consistent with my hypotheses listed in chapter 2 (section 2.5), is the lack of evidence to support a *direct* relationship between insight levels at first presentation with psychosis and risk of suicidal behaviour in the early stages of the illness, when precisely such risk is significantly higher (e.g. Palmer et al., 2005).

However, three points deserve further discussion. First, suicidal history, which was replicated as the strongest predictor of future suicidal events, including suicides (Chapter 3), in the four FEP studies presented in this thesis (Chapter 4-7), affects insight levels at first presentation. Second, the bivariate analyses from the combined UK FEP cohort (GAP and AESOP, chapter 6), which was sufficiently powered (90%), revealed treatment compliance and total insight to behave as significant predictors of suicidal behaviour, although such an association did not remain significant when multivariable analyses were carried out. Third,

depression was linked with both suicidal history and insight levels in the three FEP cohorts. And depression was also related to risk of suicidal behaviour in the AESOP sample (Chapter 5) and in the Santander cohort (Chapter 7), which is in full agreement with previous FEP studies (see Pompili et al., 2011; Challis et al., 2013). Table 8.2. below shows the associations of insight dimensions with depression across the studies included in this thesis.

Table 8.2. Depression and insight dimensions in FEP

Insight dimensions	GAP Chapter 4	AESOP Chapter 5	GAP-AESOP Chapter 6	SANTANDER Chapter 7
Recognition	+	+	-	-
Relabelling	+	+	-	n/a
Compliance	-	+	-	+
Social consequences	n/a	n/a	n/a	+
Total insight	+	+	-	n/a

GAP: Genetics and Psychosis Study (Chapter 4)
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses (Chapter 5)
+: There was a significant association. -: There was no significant association. n/a: Not applicable

Several questions arise. First, does suicidal history influence insight or is it actually a consequence of gaining insight in early psychosis? Second, why do some, but not all, patients who gain insight become depressed, which can also lead to suicidality? In other words, what underlies the relationship between insight and depression in psychosis? Third, how do insight changes in the early stages of psychosis affect risk of suicidal behaviour?

Indeed, insight has been consistently associated with depression (Mintz et al., 2003; Belvederi et al., 2015), which is known as the 'Insight Paradox' (Lysaker et al., 2007), i.e. better insight, worse depression despite the general positive associations of insight with outcome (McEvoy, 2004; Lincoln et al., 2007). However, no causality conclusions can be drawn from such a 'cross-sectional' association. Thus, although it is intuitive to think that becoming aware of having such a devastating mental illness should lead to a depressive state, including increased suicidality, which is known as the 'demoralization syndrome' (Drake et al., 1985; Drake & Cotton, 1986; Amador et al., 1996; Restifo et al., 2009); the so-called 'depressive realism model' explains how depression, which is linked with disturbed cognitions (i.e. depressed patients tend to think more pessimistically, thus being able to more easily recall negative events such as an illness, i.e. better insight), can result in greater levels of insight

(Ghaemi & Rosenquist, 2004). Furthermore, longitudinal studies suggest that insight improving is associated with better mood (Pijnenborg et al., 2013).

A different approach to better understand what underlies the relationship between insight and depression in psychosis is to examine its mediators and moderators. Previous research on this topic is limited, however. Lysaker et al. (2007) found internalized stigma to mediate such an association in a sample of schizophrenia patients, particularly in terms of functioning (Lysaker et al., 2007). More recently, Belvederi et al. (2016) tested the 'insight paradox' (Lysaker et al., 2007) in a sample of (n=89) outpatients with stable schizophrenia. Interestingly, amongst multiple insight domains, which were measured with the SUMD (Amador, 1993), only unawareness of symptoms was linked with depression, which was evaluated by the CDSS (Addington et al., 1992). Of note, low socioeconomic status, disengagement and illness severity were found to moderate the relationship between this insight domain (unawareness of symptoms) and depression, i.e. the lower the socioeconomic status and/or the lower the engagement and/or the more severe the illness, the stronger the association of insight with depression (Belvederi et al., 2016).

Based on my findings concerning the association of suicidal history, depression, insight and further suicidal events and my clinical experience, the phenomenological model of acute psychosis proposed by Conrad (1958) may shed some light on this matter. Conrad described the stages of psychosis onset in relation to the degree of insight, i.e. psychotic symptoms become more severe as insight levels decrease, which usually results in first presentation to services, when the patient is diagnosed and receives treatment. This results in symptom remission, after which insight is developed. In other words, patients first present with *symptoms*, which result in a diagnosis (*illness*) and the subsequent treatment onset with some degree of *compliance*. Interestingly, my results mirror this medical model of insight dimensions gain (symptoms → illness → treatment) with regard to suicidality. Thus, while the subject presents with more and more severe psychotic symptoms (i.e. the prodromal stage), if this psychotic state also impacts on mood leading to depression, which was linked with the content of these psychotic experiences (Upthegrove et al., 2014), such a patient is at a higher risk of attempting suicide. Indeed, those who made suicide attempts, when asked about the reasons underlying such acts, tended to describe them as coping mechanisms (e.g. Acosta et al., 2006; Harvey et al., 2008; Andriopoulos et al., 2011). As a result, the suicidal patient receives medical attention earlier, thus shortening the DUP and presenting with greater levels of insight than non-suicidal subjects (Lopez-Morinigo et al., 2014a). In keeping with this, awareness of

symptoms was found to be the more strongly associated insight domain with depression (Belvederi et al., 2016) and suicidality (Amador et al., 1996; Lopez-Morinigo et al., 2014a). After psychosis remission and completion of the diagnostic process, during which the patient is exposed to some degree of 'psychoeducation' (i.e. 'your diagnosis is that of first-episode psychosis') with a focus on treatment compliance ('you should continue taking this antipsychotic'), the depressive patient will develop insight into aspects linked with the 'need' for treatment, which also perpetuates such a depressive state (awareness of the 'need' for treatment is not the same as awareness of the 'benefits' from treatment) and the subsequent negative thinking style, thus leading to a self-perpetuating vicious circle. This is in full agreement with my findings from the three FEP studies presented in this thesis except the GAP cohort (chapter 4), which may be related to its limited statistical power (62%). Hence, these depressive-insightful patients, who are 'at risk' of suicidal behaviour at first contact with services, particularly those with previous suicide attempts, should be carefully provided with coping mechanisms in order to make different narrative judgments of the illness (Lysaker et al., 2007), i.e. to improve insight *qualitatively* rather than *quantitatively*.

Insight has been reported to evolve over the course of the illness with a tendency to improve in the early stages (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011), although these improvements appear to be less relevant in the longer-term (Ayesa-Arriola & Morinigo et al., 2014). Although my research did not evaluate insight over the follow-up (see section 8.8.b.6, below), previous literature (Bourgeois et al., 2004; Pijnenborg et al., 2013; Barrett et al., 2015) suggests that insight improvement is associated with less depression and potentially less suicidality, which definitely warrants further research as discussed further below.

8.6. – Predictors of suicidal behaviour in psychosis

Chapter 3 presented the findings from a large dataset of patients with SSD under secondary mental healthcare in SLaM. Interestingly, young age at first contact, suicidal history and suicidal ideation emerged as the main predictors of suicide.

Chapter 4, which was based on data from the GAP FEP study, reported four predictors of suicidal behaviour over the follow-up, namely treatment compliance, age at first contact, living alone and a previous suicidal history. However, only living alone and suicidal history remained significant in the multivariable Cox-regression model. Chapter 5, which described the findings from the AESOP study, revealed previous suicide attempts, alcohol use, executive dysfunction and depression to be associated with an increased risk of suicidal behaviour over the 10-year follow-up, although only suicidal history and depression survived the multivariable regression models. Unsurprisingly, chapter 6, which presented the analyses from the GAP-AESOP combined cohort of FEP patients revealed suicidal history and executive dysfunction to be linked with suicidal behaviour risk.

Finally, regarding the Santander cohort detailed in chapter 7, the bivariate analyses reported younger age at first presentation, suicidal history, family history of psychosis, poor premorbid adjustment and depression to be related to risk of suicidal behaviours over the follow-up. Of note, poor premorbid adjustment, suicidal history, depression and age at first presentation survived the multivariable regression models.

A summary of the above predictors of suicidal behaviour in early psychosis is shown in table 8.3., below. In brief, younger age at first presentation, suicidal history and depression were replicated to be the strongest predictors of suicidal behaviour in early psychosis, which is consistent with previous literature (e.g. Hawton et al., 2005; Challis et al., 2013).

Of relevance, no insight dimension at baseline predicted risk of suicidal behaviour in the multivariable analyses based on data from these FEP samples, although the Santander study found insight into the social consequences of the illness and insight into the need for treatment to be associated with an increased risk of suicidal behaviour over the 3-year follow-up period.

Table 8.3. Predictors of suicidal behaviour in psychosis

	CRIS Chapter 3	GAP Chapter 4	AESOP Chapter 5	GAP-AESOI Chapter 6	SANTANDER Chapter 7
Age (young)	+	-	-	-	+
Living alone	-	+	-	-	-
Marital status	-	-	-	+	-
Suicidal history	+	+	+	+	+
Suicidal ideation	+	n/a	n/a	n/a	n/a
Poor premorbid adjustment	n/a	n/a	n/a	n/a	+
Cognition	-	-	-	+	-
Depression	-	-	+	-	+

CRIS: Clinical Record Interactive Search (Chapter 3)
GAP: Genetics and Psychosis Study (Chapter 4)
AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses (Chapter 5)
+: There was a significant association. -: There was no significant association. n/a: Not applicable

8.7. – Integration of findings

In summary, Chapter 3 showed that older age at first contact with services and lack of suicidal ideation and suicidal history identified those patients with schizophrenia and related disorders who are less likely to take their lives, bearing in mind that the lifetime suicide risk in a high-risk group of patients with psychosis is still very low (2-5%) (Dutta et al., 2010; Palmer et al., 2005). The fortunate rarity of the outcome is what limits the predictive potential of any modelling.

However, in the light of the multivariable Cox regression analyses from the experimental chapters (4-7) concerning the role of insight dimensions in risk of suicidal behaviour in early psychosis, two major conclusions can be drawn. First, I found no evidence to suggest that there is a *direct* link between insight levels in FEP and risk of suicidal behaviour in the immediate years ahead. Second, suicidal history and depression were the strongest predictors of suicidal behaviour, which was in line with previous literature. Given that both suicidal history and depression correlated with insight levels at baseline, this may explain, in large part, the apparent relationship between insight dimensions and suicide risk. How may we integrate these findings? Figure 8.1. below illustrates the hypothesised model (see Chapter 2, section 2.5) of the relationship between insight dimensions and risk of suicide behaviour in FEP which has been tested in this thesis. Figure 8.2 shows, however, the model based on the investigation results.

The development of psychotic symptoms from the prodromal stage is associated with an impact on mood in some, but not all, patients, which has been related to the content of the psychotic phenomena (Upthegrove et al., 2016). These patients would therefore be at a higher risk of making suicidal acts, which was replicated to be the strongest predictor of future suicidal events. Suicidal antecedents help to gain awareness of illness and symptoms relabelling ('that is why I attempted to take my life, I was hearing voices, I must be ill'), which is consistent with the results from the GAP-AESOP combined cohort. Thus, during the recovery phase this depressive state would lead these patients to thinking more pessimistically, consistent with the so-called depressive realism model (Ghaemi & Rosenquist, 2004), thus becoming more aware of the negative aspects of the illness such as its social consequences and the 'need' for treatment, which also perpetuate the depressive cycle. In other words, as postulated, depression or at least low mood, and suicidal history explain, in large part, the apparent association of insight with suicide risk in psychosis. Of course, other factors play a part in such a complex phenomenon.

Figure 8.1. Hypothesised model to be tested in this thesis.

Red arrows indicate increased risk and green arrows show reduced risk.

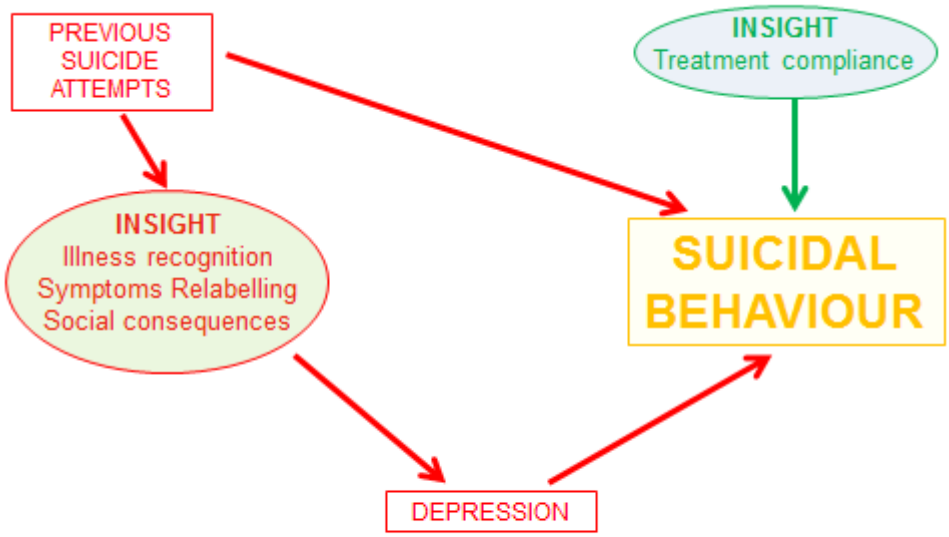
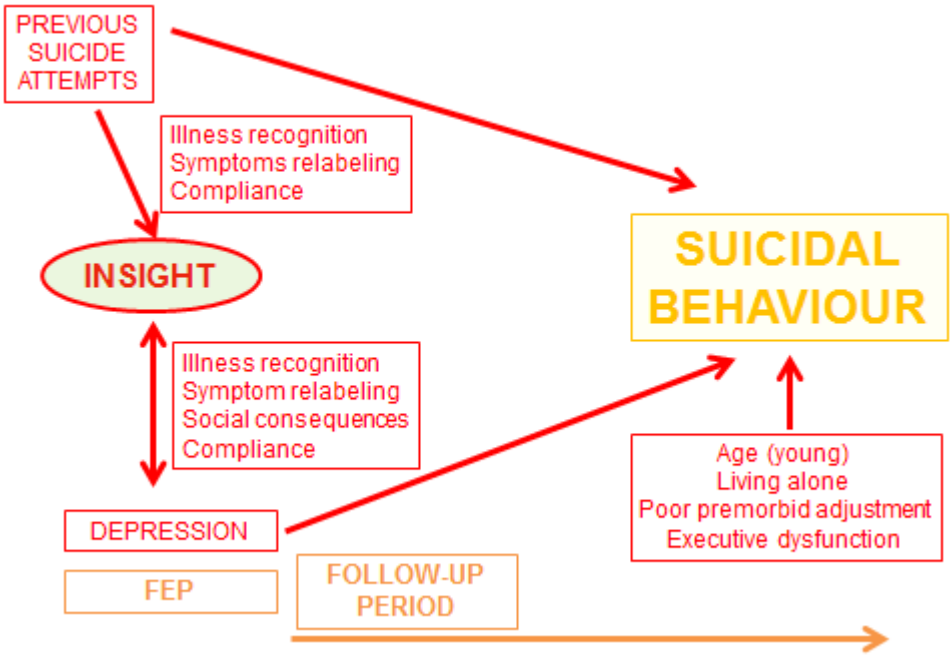


Figure 8.2. Model based on the thesis findings

Red arrows represent increased risk



8.8. – Strengths and limitations

8.8.a. – Strengths

Chapter 3 provided information on real-world data concerning suicide by patients with schizophrenia and related disorders receiving secondary mental health care in our catchment area. In particular, a large case register (currently accessing records on over 250,000 patients) linked to national mortality data was used. Also, the sample was very likely to be representative since only a tiny proportion of patients living in South-East London receive private mental health care and a wide range of demographic and clinical variables, including service use-related factors and specific scales such as HoNOS and 'risk assessment', were analysed. More specifically, the use of a large case register allowed the investigation of a rare phenomenon such as suicide completion in patients with schizophrenia spectrum disorders. In particular, up to 96 of such subjects were identified.

With regard to my main research question, i.e. the role of multiple insight dimensions at first presentation of psychosis, I used up to three different FEP cohorts, including long follow-up periods (up to 10 years in the AESOP sample) in order to capture a sufficient number of suicidal events. It is noteworthy that these FEP samples formed part of large scale FEP studies, involving recruitment from many wards across a large catchment area, conducted by many research workers and encompassing an intensive study battery, which used validated scales to measure a wide range of baseline variables, including insight. Before discussing the disadvantages of this type of project in the next section, it is important to acknowledge that it would have been unfeasible to collect this amount of data within the context of a smaller study. The increased resources of the studies made it possible to reach the widest possible range of patients and complete a large number of assessments on each of them, thus increasing statistical power and external validity.

Indeed, the statistical power of the above samples ranged from 62.5% to 96.7%, thus suggesting that the lack of associations between insight levels and risk of suicidal behaviours was not due to insufficient power (Type II error), or at least this was unlikely. Furthermore, the recruitment of FEP samples from two different countries such as Spain and the UK permitted me to address potential cultural issues associated with suicide risk in psychosis, thus increasing further the generalisability of the findings from this research. In particular, the consistency between the findings regarding my research question suggests that the confounding role of depression and previous suicide attempts in the apparent relationship between insight and suicide risk in psychosis cannot be attributed to cultural factors.

8.8.b. – Limitations

This investigation, though both consistent with much previous work and delivering several novel findings, has some limitations. Some of these have been addressed throughout the thesis. However, some more general limitations shall be discussed here.

8.8.b.1. – Bias and confounding

All the individuals who took part in the above studies, including cases and controls, received mental health care from publicly-funded secondary services, which introduces a potential selection bias since those patients with psychosis who received care from the general practitioner or in the private sector were not recruited. However, the number of these cases is likely to be small both in Spain and in the UK. Of note, the potential hospital bias was avoided by including both out- and inpatients in the above studies, although most of the participants were inpatients, which applies to the vast majority of research in FEP.

Another potential systematic error concerns those suicidal behaviours, including deaths from suicide, outside the UK (or Spain in the case of the Santander patients) or simply unreported (e.g. homeless people), which therefore were not captured. Given the attrition rates at the end of the studies (around 15-20%), which were consistent with previous prospective FEP studies (e.g. Robinson et al., 2010), this limitation should not have affected the findings significantly.

8.8.b.2. – Generalisability

This research work included three cohorts of FEP patients from two different countries (Spain and the UK) which were followed-up over prolonged periods of time (from 3 to 10 years). While this methodology made the overall findings more generalizable, some caution should be taken when comparing results between the included studies; for instance, the level of urbanicity differed significantly between the Santander cohort and the UK samples. In addition, procedures for case ascertainment vary between these two countries, which may also reflect preferences in suicide recording. Of course, the findings from this investigation cannot generalise to all countries and settings across the world.

In addition, it remains a matter of debate whether suicide attempters and completers represent similar or different populations. In particular, based on some differences between

these two groups, particularly in terms of personality-related variables (Giner et al., 2013), some authors have suggested that, statistically speaking, suicide completers may represent the 'outliers' of suicidal groups (mainly formed of suicide attempters), which may also partially explain the limited ability to predict suicide completion both in research and in the clinical setting (de Leon et al., 2015). However, no such differences were replicated in psychotic patients (Innamorati et al., 2008; Giner et al., 2013), which provides further support to the methodology used in this thesis.

8.8.b.3. – Sample size and power

The power calculations detailed in chapters 4, 5, 6 and 7 showed that while the GAP (62%) and AESOP (75%) cohorts were underpowered to detect clinically meaningful differences in insight variables (with an effect size of 0.33) across groups (suicide attempters vs. non-attempters), provided such differences exist, the combined FEP cohort resulting from merging GAP and AESOP samples and the Santander cohort were both sufficiently powered (over 90 and 98%, respectively), thus making a Type 2 error unlikely. In this investigation, a Type 2 Error would be of particular concern since I aimed to demonstrate the 'null' hypothesis, i.e. the lack of *direct* associations of insight levels with suicide risk.

8.8.b.4. – Missing data

The length of the battery administered to patients (often well over 10 hours) meant that many were unable to complete all tasks. One problem this caused was patchy data, where completion rates were different between measures. Consequently, whilst a high number of recruited patients completed at least one insight measure (main inclusion criterion), a smaller number completed all the assessments. This meant that statistical power was considerably reduced because in the final models only those patients with all the variables tested were included. As a result, bias may have been introduced if the tendency to have a particular missing variable was related to insight and the link between insight and suicide risk. Intuitively, one may expect that those with a lower number of missing variables were more 'compliant' with the study procedure, which clearly links with insight.

This also raises a general limitation to all studies on insight, which is the ethical requirement of providing informed consent. In particular, it should be noted that generally speaking all study participants consented to take part. Hence, those who declined probably

had poorer insight levels and findings cannot apply to these subjects. For instance, approximately 44% of patients approached to participate in the GAP project declined our invitation, and it is possible that they were systematically different from those who did take part. However, schizophrenia patients' willingness to participate in research was not found to be influenced by insight according to one survey (Kim et al., 2009).

8.8.b.5. – Insight assessment

Although insight assessments were conducted as early as practicable during the admission (most of the participants were inpatients), in some cases there were some delays between completion of insight assessment and other measures, hence adding statistical noise to the data. Symptom measures in particular may be affected by this, as they may change significantly over the course of assessments. However, symptoms severity (PANSS, SCAN, SAPS, SANS) and insight tended to be evaluated at the same time in most cases. Also, insight may well change over time, although there is evidence to suggest that longer-term insight tends to be relatively stable (Ayesa-Arriola & Lopez-Morinigo et al., 2014). For example, a patient who had very little insight when completing the SAI-E, may have had better insight

Furthermore, there were multiple investigators administering and scoring assessments. Whilst every care was taken to ensure that researchers were thoroughly trained in each assessment, with 'top-ups' of training regularly provided, and relevant experts always available to advise as appropriate, it is possible that differences between investigators existed, particularly for less structured assessments such as the SAI-E and the PANSS. Although this is unlikely to have had any systematic effect, it may have weakened the size of any genuine effects that existed in the data. Also, researchers were not blind to other measures. For example, a researcher rating the PANSS very high (i.e. the patient is severely psychotic) may have a tendency to underscore insight.

8.8.b.6. – Changes of insight and other variables

Baseline predictors, including insight variables, may have changed over the follow-up period. Hence, their associations with suicide risk should be taken cautiously, particularly regarding late suicidal events, which in some cases occurred up to 10 years after the study inception. However, it should be noted that my research interest here, which was driven by my clinical experience, was investigating whether insight levels at the time of first presentation to services with psychosis (i.e. when FEP patients are more comprehensively evaluated in the clinical setting) predicted suicide risk given the clinical implications on insight development / management if such an association was demonstrated, which is discussed further in section 8.9., below. Also, by conducting survival analyses instead of logistic regression, not only was the likelihood of the event taken into account, but also the time to event (and time to non-event or end of the study as appropriate), thus lessening the above potential limitation.

8.8.b.7. – Non-evaluated variables

Other non-tested factors might contribute to both insight and suicide risk in psychosis, such as premorbid personality (Lysaker et al., 1999; Ritsner et al., 2007; Campos et al., 2011), neurobiological variables (David et al., 2012; Mann et al., 2003) and medication effects (Pijnenborg et al., 2015; Meltzer et al., 2003; Bourgeois et al., 2004), which are discussed further in section 8.10, below, as potential areas for future research.

8.9. – Clinical implications of this investigation

This research work would be completely theoretical if the findings could not contribute to improving patient's outcomes, which in this case would equate to preventing suicide in patients with psychotic disorders, or at least reducing this risk. Although thankfully suicide is an uncommon outcome in psychosis, with a lifetime risk currently estimated at approximately 2-5% (Dutta et al., 2010; Palmer et al., 2005), even in high-risk patients such as those receiving secondary mental healthcare, it is worth considering that these fatal events tend to occur early in the course of the illness, thus representing a high number of life years lost. In other words, preventing just one patient with psychosis from suicide may result in him/her living for up to 30 more years (Lopez-Morinigo et al., 2016).

8.9.a. – Suicide prevention in psychosis

First of all, it is worth making a point on what we mean by suicide *risk*. In the very first paragraph of this thesis (Chapter 1), I stated that 'suicides are preventable' (WHO, 2016), which is indeed an assumption prerequisite for this type of research.

In short, suicide prevention means reducing *risk*. According to the English Oxford Dictionary, *risk* can be defined in terms of 'possibility' or 'probability', but also regarding the consequences of the occurrence. In other words, risk should be conceptualised as the inverse relationship between 'likelihood of the event' and 'severity of the consequences of the event'. For instance, the 'suicidal spectrum' encompasses from suicidal ideation (high risk in terms of likelihood, low risk given its consequences) to suicide completion (low risk in terms of likelihood, high risk given the irreversible consequences) (Bebbington et al., 2010).

According to the WHO, there are a number of measures that can be taken at population, sub-population and individual levels to prevent suicide and suicide attempts (WHO, 2016):

- Reducing access to the means of suicide (population-level).
- Reporting by media in a responsible way (population-level).
- Introducing alcohol policies to reduce the harmful use of alcohol (subpopulation-level).

- Early identification, treatment and care of people with mental health and substance use disorders, chronic pain and acute emotional distress (subpopulation-level).
- Training of non-specialized health workers in the assessment and management of suicidal behaviour (subpopulation-level).
- Follow-up care for people who attempted suicide and provision of community support (individual-level).

Although this investigation focused on a high-risk group (patients with a FEP), the overall low positive predictive value of a combination of suicide risk factors reported in chapter 3 (Lopez-Morinigo et al., 2016) suggests that population-level strategies may be more useful. In particular, I replicated that hanging and jumping (from a height or in front of a vehicle) were the most common suicide methods in this SSD sample. In keeping with a recent Lancet review of suicide prevention measures (Zalsman et al., 2016), I suggest that installation of physical barriers on bridges, tall buildings and railway stations, particularly those near psychiatric hospitals, may prevent patients with SSD from suicide as well as the general population (Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016).

A more challenging issue is suicide prevention at an individual level in the clinical setting (Lopez-Morinigo et al., 2016). In this regard, the main implication of this investigation is that insight, which is strongly linked with better outcomes in psychosis (McEvoy et al., 2004; Lincoln et al., 2007), does *not* increase suicide risk despite common assertions to the contrary. Hence, these results, although pending independent replication, should help clinicians to focus on insight improvement strategies, which indeed warrants further research (see section 8.10.a. below).

In addition, the role of previous suicide attempts and depression in the risk of further suicidal events in early psychosis was replicated, particularly amongst those younger patients at first contact with services.

In particular, the presence of suicidal antecedents appears to be a useful marker to identify those 'at-high-risk' patients, who should therefore be more closely monitored after first presentation with psychosis (i.e. individual-level prevention). Furthermore, as alluded to above, I speculate that such suicidal history informs us about the patient's personality and coping mechanisms. Specifically, I demonstrated that these suicidal

patients tended to be less aware of the need for treatment (see chapter 7, Santander-based). In other words, these individuals seem to deal with problems themselves, which links to the general tendency of psychotic patients not to report suicidal ideation (Bakst et al., 2009). Hence, suicide prevention at an individual level seems to be about predicting how our patients will react to specific potential (i.e. unpredictable) stressors, such as a relationship breakup, which is related to measurable factors such as current mental state or premorbid personality (i.e. coping mechanisms style), about which suicidal history tells us much. More specifically, being depressed (current mental state) or having a tendency to becoming depressed (i.e. personality) appears to play a major role in suicide risk in psychosis. Accordingly, a more detailed discussion about suicide in psychosis is provided below.

8.9.b. – Depression and insight in psychosis

The role of depression in suicidality in psychosis was replicated in this investigation, which is in full agreement with previous literature (Altamura et al., 2003; Hawton et al., 2005; Bertelsen et al., 2007; Flanagan and Compton, 2012; Harvey et al., 2008; Kontaxakis et al., 2004; Barrett et al., 2010a; Barrett et al., 2010b; Pompili et al., 2011; Challis et al., 2013).

Specifically, in my literature review summarised in chapter 2 and published (Lopez-Morinigo et al., 2012), I found hopelessness to be associated with suicidality, particularly in FEP samples. On the other hand, Chapter 3 (based on data from CRIS) showed that hopelessness was relatively uncommon amongst those patients with SSD who ended their lives, which led me to speculate that the impact of hopelessness, and probably depression in a broader sense, on suicide risk, appears to be stage-related, i.e. more relevant in early phases of psychosis, consistent with previous literature (Pompili et al., 2011; Ayesa-Arriola et al., 2015).

However, it remains unclear whether 'depression' in early psychosis represents a symptomatic domain in its own right (Peralta et al., 2013) or a psychological reaction to the social consequences of the psychotic illness onset (Drake & Cotton, 1986). Thus, a recent 12-month follow-up first-episode psychosis study found that while malevolent voices, use of safety behaviours and subordination to persecutors were associated with depression in the acute FEP, post-psychotic depression was linked to loss, shame, low level continuing positive symptoms and longer duration of untreated psychosis (Upthegrove et al.,2014).

In line with the results from this Santander cohort, a previous first episode study from our group found an association between suicidal behaviour preceding first contact with services and depression at that point (Lopez-Morinigo et al., 2014a; Chapter 4). Also, depression in the prodromal stage was reported to predict both suicidality at first presentation and further depressive episodes both in the acute and recovery stages of FEP (Upthegrove et al., 2010). This association seems to challenge, to some extent, the so-called demoralization syndrome (Drake and Cotton, 1986) since depression in early psychosis appears to behave as a trait-like phenomenon (Upthegrove et al., 2010) rather than a psychological reaction to the social consequences of such a devastating illness. Overall, depression seems to play a crucial role in suicide risk in schizophrenia (Hawton et al., 2005) and FEP (Pompili et al., 2011). However, there are few guidelines on the management of depression in schizophrenia and related disorders (Siris, 2000; Siris, 2001; NICE, 2015).

With regard to the theoretical conceptualisation of depression in schizophrenia, Birchwood postulated up to three distinct pathways: depression which is intrinsic to psychosis, depression which is a psychological reaction to the diagnosis and depression as "*smoking gun evidence*" of childhood trauma (Birchwood et al., 2005). Specifically, the second pathway received stronger support from research, which can be summarised as, '*it is the way a person appraises the meaning and significance of their psychotic experience, including their subordinate relationship to voices, or persecutors and the impact of the diagnosis on social status that underlies the development of depression*' (Upthegrove et al., 2016).

One clinically relevant aspect to mention concerns the difficulties that clinicians so frequently find in distinguishing negative and depressive symptoms (Siris, 2001; Upthegrove et al., 2016).

In 2003, a classic meta-analysis of 40 studies examining associations of insight with psychopathology found depression to have a positive correlation with insight, although the effect size was rather small (r=0.18) (Mintz et al., 2003). Interestingly, a more recent meta-analysis (Belvederi et al., 2015) looking at the association of depression with insight from a multidimensional approach failed to link compliance with depression, which led me to formulating the hypothesis (H5) (Chapter 2, section 2.5) that compliance would reduce suicide risk.

However, prospective studies do tend to show that depression improves as insight levels increase (Bourgeois et al., 2004; Pijnenborg et al., 2013; Barrett et al., 2015), which suggests that this complex association appears to be dynamic in nature, which is intuitive. More specifically, time is needed for the patient to make different judgments of the nature of their mental illness, from being made aware of the 'need' for medication to acknowledging the 'benefits' from a treatment plan (in the broadest sense), in which patients with psychosis should be able to get fully involved (NICE, 2015).

8.9.c. – Implications on services provision

Organisational factors and service provision changes were demonstrated to affect suicide rates at a national level in the UK (Kapur et al., 2016). For instance, it is noteworthy the reduction in inpatient suicides, which was mainly due to the focus on ligature risk assessment/management, may have occurred at the price of an increase in post-discharge suicides (Kapur et al., 2013). Nevertheless, there has been an increase in the number of suicides by patients with schizophrenia in the UK since 2008 (NCISH, 2015).

With regard to psychosis, based on preliminary research showing the detrimental effects of delaying treatment (Johnstone et al., 1986) on outcome, over the last two decades there has been a growing interest in the implementation of early intervention services (EIS) for patients with psychosis (McGorry et al., 1996).

In the UK the first EIS started in Birmingham in 1990. Since 2001 the development of EIS has become a priority across the UK as a result of several reasons, including the rise of community care, the move towards control as well as care in the community, user and carer concerns, the increasing evidence of unacceptably long durations of untreated psychosis (DUP) and the benefits from early diagnosis and treatment (DoH, 2001). Specifically, the Policy Implementation Guidance on Early Intervention (DoH, 2001) suggested that EIS should be able to:

- Reduce the stigma associated with psychosis and improve professional and lay awareness of the symptoms of psychosis and the need for early assessment
- Reduce the length of time young people remain undiagnosed and untreated.
- Develop meaningful engagement, provide evidence-based interventions and aid recovery during the early phase of illness.
- Facilitate development and provide opportunities for personal fulfilment including social life and employment and training opportunities.
- Provide a user-centred service that is a seamless service available for those from 14–35 years of age.
- At the end of the treatment period (up to 3 years), ensure that the care is transferred thoughtfully and effectively.

Overall, mixed results have been reported regarding the effect of EIS on suicide rates. In particular, it seems that the initial protective effect disappears once the early intervention

period ends, which has been particularly examined in Scandinavian countries such as Denmark (Nordentoft et al., 2002; Bertelsen et al., 2008) and Norway (Melle et al., 2006; Melle et al., 2010), and in Canada (Goldberg et al., 2006) and Australia (Harris et al., 2008). However, extending the treatment period has been shown to reduce suicide rates in Hong Kong when compared with standard care (Chan et al., 2014). Not only UK-based studies are needed in this area but also, a meta-analysis in order to get a better understanding of the real effect of EIS on suicide rates. While the above negative results may have been due to insufficient statistical power given the very low number of suicides identified in the studies, suicide attempts are a more frequent measurable outcome for more powered studies.

Of relevance, the case-fatality estimated in the FEP studies presented in this thesis ranged from 1.5% (Santander cohort) to 2.7% (GAP and AESOP studies), which were considerably lower than that reported by Palmer and colleagues in their 2005 seminal meta-analysis, which was 4.9% (Palmer et al., 2005). While participants in these FEP studies, all of whom were receiving care from EIS, were followed-up for up to 10 years and some suicides may occur at later stages (Dutta et al., 2010), based on these findings there are grounds to consider that EIS may reduce suicide rates in psychosis patients, although more prolonged follow-up periods are needed.

However, a number of suicide attempts in the FEP samples presented in this thesis occurred before the onset of psychosis as rated by the so-called DUP (for instance, up to 43% in the GAP study), thus supporting the role of 'at-ultra-high-risk' services in suicide prevention. In this regard, it should be noted that in such a prodromal state depression behaves as the only significant predictor of suicidal behaviour (Nielssen & Large, 2009; Andriopoulos et al., 2011), which is consistent with a previous FEP study which demonstrated that indeed depression appears to precede the onset of psychosis (Upthegrove et al., 2010). Nevertheless, the benefits from EIS are yet to be established (Castle & Singh, 2015), particularly taking into account the current financial context (David, 2011).

8.10. – Directions for future research

Throughout this research work, I have become aware of a range of putative factors associated with suicidal behaviour in psychosis which were not evaluated in this study, such as insight changes, suicidal behaviour in prodromal stages of psychosis and premorbid variables, stigma, neurobiological variables, metacognition and the use of new technologies.

8.10.a. – Insight changes

Insight has been reported to be a dynamic phenomenon, which improves over the early stages of the psychotic illness (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011; Parellada et al., 2011), although longer-term studies appear to suggest a ceiling effect, i.e. poor insight in psychosis patients appears to be a 'trait' rather than a state associated with acute psychosis (Ayesa-Arriola & Lopez-Morinigo et al., 2014). Nevertheless, longitudinal studies found no evidence to link insight improvement with increased suicidality (Bourgeois et al., 2004; Pijnenborg et al., 2013), which is in full agreement with the findings from this investigation.

Regretfully, I could not re-evaluate insight in participants over the follow-up periods, which would require face-to-face interviews given the limitations associated with self-rated scales such as the Birchwood Insight Scale (Birchwood et al., 1994), namely a tendency to recall bias.

Certainly, intervention studies are needed to clarify the real associations of insight levels with risk of suicide; for instance, if an insight improving intervention was shown to reduce suicidality. In particular, antipsychotic treatment has been demonstrated to increase insight levels (Pijnenborg et al., 2015) and reduce suicide rates at a population-level (Torniainen et al., 2015), while as far as I know, no 'cognitive-behaviour therapy for psychosis' study looking at suicidality and insight as outcomes has been conducted to date.

8.10.b. – Suicidal behaviour in prodromal stages

I found a high number of suicidal events prior to first presentation to services. However, little research has been conducted in this stage of the illness with suicidal behaviour as an outcome (see Andriopoulos, 2011). Hence, there are grounds to consider that a number of people with undiagnosed psychosis die from suicide before first contact with services. Psychological autopsy studies of deceased adolescents with a focus on psychosis screening are warranted for this.

8.10.c. – Stigma

Stigma, which prevents patients from receiving proper care (Alonso et al., 2007), may contribute to suicide risk in patients with SSD who disengage from secondary mental health services (Thornicroft & Mansella, 2013). Nevertheless, more research is needed to test whether anti-stigma campaigns, such as the England-based 'Time to Change' (Henderson & Thornicroft, 2009) or the worldwide 'Depression: Let's talk' (WHO, 2016), can reduce suicide rates both at a population level and in high-risk groups such as mental health service users with SSD (Rüsch et al., 2014).

8.10.d. – Neurobiological variables and medication

After the seminal contribution by Mann et al. (1999), who proposed a diathesis-stress model of suicide detailed in chapter 1 (section 1.2.b), a number of studies have investigated the role of different neurobiological mechanisms with a focus on serotoninergic systems (Mann et al., 2003; Oquendo et al., 2014). However, overall results have been inconclusive, which led to a 2015 editorial warning against the limitations of Mann's original model and highlighting the role of non-medical psychosocial factors in suicide, which cannot be predicted (de Leon et al., 2015).

To the best of my knowledge, no study has specifically investigated the neurobiology of suicidal behaviour in psychosis to date. In this regard, it may be worth looking at the neurobiological mechanism of action underlying the well-demonstrated anti-suicidal effects of clozapine on patients with schizophrenia (Meltzer et al., 2003; Bourgeois et al., 2004), including a Cochrane meta-analysis (Asenjo et al., 2010). Interestingly, clozapine was also reported to improve insight when compared with classic antipsychotics in a non-randomized trial of

(n=22) schizophrenia patients (Pallanti et al., 1999). Moreover, data from the InterSePT study showed that over the 2-year follow-up, insight improved while risk of suicide decreased (Bourgeois et al., 2004). Generally speaking, antipsychotic exposure has been associated with reduced suicide rates in a nation-wide study from Sweden (Torniainen et al., 2015), which provides additional support for the role of engagement in reducing suicide risk. However, more modest results were reported on the benefits of medication on insight (Pijnenborg et al., 2015). Furthermore, as alluded to above (section 8.10.a), the main research question investigated in this work might be properly answered if a specific antipsychotic (but also any non-pharmacological intervention) was demonstrated to improve insight and reduce suicidality. To the best of my knowledge, this study is yet to be carried out.

8.10.e. – Premorbid variables

Some aspects of premorbid personality have been linked with insight levels in schizophrenia (Lysaker et al., 1999; Ritsner et al. 2007) and FEP (Campos et al., 2011). More specifically, sociopathic and schizoid personalities were associated with lack of insight at 6 months after FEP (Campos et al., 2011). Also, passive-dependant personality traits predicted suicide attempts at 6-month follow-up in a FEP sample (Canal-Rivero et al., 2016). Hence, further studies looking at the mediating effects of premorbid personality on the relationship between insight and suicide risk in early psychosis are needed.

Moreover, premorbid variables should be carefully assessed as they appear to mediate the association of insight with suicide risk; for instance, the higher the premorbid functioning, the more demoralizing insight will be and therefore, more strongly linked with suicidality (Levine et al., 2010).

8.10.f. – Metacognition

In Chapter 1 (section 1.3.f.) I commented on the different theories proposed to explain what underlies poor insight in psychosis. Despite much attention being paid to neurocognitive deficits on the basis of its similarities with anosognosia observed in neurological disorders (Babinski, 1914), a meta-analysis of 35 studies in 2006 reported overall modest results (Aleman et al., 2006). This meta-analysis' authors suggested in the very last paragraph of the article (Aleman et al., 2006) that other variables may contribute to insight, such as metacognition, which has attracted much research attention since, particularly so-called cognitive insight (Beck et al., 2004), which is linked with outcome in FEP (e.g. O'Connor et al., 2013).

This focus on metacognition also resulted in promising results from non-randomized metacognitive therapy clinical trials, which showed an improvement in both insight and depression (e.g. Favrod et al., 2011). Further intervention studies testing metacognitive therapies should also include suicidal behaviour as an outcome measure. Indeed, cognitive insight appears to mediate the relationship between clinical insight and depression (Palmer et al., 2015), which based on my findings explains the apparent association of insight with suicide in psychosis.

8.10.g. – New technologies

According to the International Communication Union (ICU), in 2016 there are over 7 billion mobile phone subscriptions worldwide and approximately half of these are mobile-broadband subscriptions, i.e. smartphones with Internet access (ICU, 2016).

The use of communication technologies in health care and public health is known as Mobile health (mHealth) (Free et al., 2010), which has been the subject of extensive research on a wide range of topics, including suicide (Vahabzadeh et al., 2016). However, the legal regulations are far from clear (Armontrout et al., 2016) and evidence on suicide prevention is still limited (Zalsman et al., 2016). Moreover, concerns have been voiced regarding the potential effect of the Internet on increased suicide risk (Aboujaoude, 2016), although this has not been confirmed yet.

From a research point of view, web-based datasets integrating data from different sites and countries appear to be promising tools to investigate suicide, particularly given its rare occurrence, and its risk and protective factors (Lopez-Castroman et al., 2015b). In addition, mobile phone and web-based text messaging may represent a useful tool to monitor suicide risk (Berrouiguet et al., 2016), particularly to follow-up suicide attempters (Berrouiguet et al., 2014). For instance, the classic suicide note may have been substituted by a message left on this new media, which clinicians should discuss with patients and carers when assessing self-harm in the emergency department (Barrett et al., 2016).

However, I have my reservations about the use of new technologies in patients with psychosis due to the potential increased paranoid thoughts associated with such a close monitoring, which may also raise ethical issues.

8.11. – Concluding remarks

Suicide is an uncommon outcome even in a high-risk group such as patients with psychosis receiving secondary mental healthcare (Lopez-Morinigo et al., 2016). As a result, a successful approach for suicide prevention in early psychosis is likely to require a combination of population-level measures such as means restriction with interventions on such a high-risk group (Dutta et al., 2010; Lopez-Morinigo et al., 2014b; Lopez-Morinigo et al., 2016), including improving insight measures based on this research.

For instance, EIS appear to play a crucial role in reducing suicide rates in such a high-risk period (Fedyszyn et al., 2014; Chan et al., 2015). However, the onset of psychosis may be 'too late' to prevent some suicidal events. Alternatively, universal school-based interventions appear to be a promising strategy to tackle suicide both in young adolescents at high-risk of psychosis and in the general population (e.g. Kelleher et al., 2012). These findings appear to provide further support for my assertion, which is now evidence-based (Lopez-Morinigo et al., 2016), that suicide, although *unpredictable* at an *individual-level*, particularly in those suffering from psychosis, seems to be *preventable* at a *population-level.*

In particular, this research does not support the commonly held view among clinicians that insight, which is linked with positive outcomes in psychosis, increases suicide risk. Moreover, based on my findings it seems that suicidal history and depression explain the apparent association of insight with suicide risk, which may prevent patients with psychosis from insight improving interventions and the subsequent positive outcomes associated with insight such as reduced rehospitalisations and better psychosocial functioning. Also, insight improving interventions appear to reduce suicidality (Pijnenborg et al., 2013), which requires further research. Hence, I hope that all this work can have a positive impact on patients' outcomes, particularly in terms of suicide prevention.

Insight in psychosis is strongly linked with better outcomes (Amador & David, 2004; Lincoln et al., 2007) and this need not occur at the price of increased suicidality as previously thought, which is the main contribution of this work. In short, it seems that 'painful truth is better than a pleasant lie' (McGill, 2015). And as it is commonly said in the UK: 'the sooner (the truth is understood), the better'.

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Appendix 1 – Ethical approval of the CRIS project

NHS
Health Research Authority

NRES Committee South Central - Oxford C
Bristol REC Centre
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421389
Facsimile: 0117 3420445

04 July 2013

Professor Robert Stewart
South London and Maudsley NHS Foundation Trust
BRC Nucleus, PO Box 92, Institute of Psychiatry
De Crespigny Park
London
SE5 8AF

Dear Professor Stewart,

Title of the Database:	**South London and Maudsley Biomedical Research Centre Case Register**
REC reference:	**08/H0606/71+5**
IRAS project ID:	**130902**

The Research Ethics Committee reviewed the above application at the meeting held on 28 June 2013. Mr Matthew Broadbent attended to discuss the application on your behalf.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Ms Rae Granville, nrescommittee.southcentral-berkshire@nhs.net.

Ethical opinion

After the Committee's initial discussions Mr Matthew Broadbent was invited to join the meeting on behalf of the Chief Investigator to clarify the following issues:

1. The Committee observed that this database was a valuable tool. It queried if the database had changed since its creation. Mr Matthew Broadbent replied that studies using this database had had an impact on relevant clinical services. He informed the Committee that the databases linkage to statutory and non-statutory services had added to the quality of the data but that the overall database had not changed.

2. The Committee asked Mr Matthew Broadbent if there was a record of how many studies had been undertaken and completed. Mr Matthew Broadbent explained that

applicant's studies were approved by a sub-committee. Overall 140 studies had been approved and 20 of these have published. He added that 60-70 of these studies were completed audit projects.

3. The Committee commented on the data identification risk. It questioned how you reduced the risk of releasing identifiable data. Mr Matthew Broadbent replied that there was always the risk that the database contained identifiable data. However, the database sub-committee would flag any searches that could locate identifiable data and it monitors the possibility of research that could select identifiable individuals or groups. In these cases blocks are placed to reduce this risk. He agreed that some research studies, on infanticide for example, would be of higher risk but assured the Committee that the research would either be blocked or extra procedures would be put in place to avoid identification.

4. The Committee commented on the twenty studies published. It asked why so few studies were published. Mr Matthew Broadbent replied that this was due to a combination of student projects and projects that have received extensions. Some of studies had been abandoned as the research had proved more difficult than expected. He explained that they currently had a core of academics that used the data regularly and knew the data well. Mr Matthew Broadbent added that the database team also were more comfortable with the data and could provide advice and guidance to researchers.

5. The Committee requested further information on the database linkages and the safety of these linkages for the data. Mr Matthew Broadbent replied that each linkage with a health database required numerous approvals from the Ethics Committee, Department of Health, Department of Education etc. and he assured the Committee that these linkages were secure.

The members of the Committee present gave a favourable ethical opinion of the above research database on the basis described in the application form and supporting documentation.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Databases set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research database.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		07 May 2013

Other: CV - Prof R Stewart		07 May 2013
Other: Paper in Press on CRIS de-identification	20130507	07 May 2013
Other: SLAM Patient Information Leaflet	20130507, v1	07 May 2013
Other: SLAM CDLS SLSP s251 application	1	07 May 2013
Other: CRIS Security Model	20130507, v1	07 May 2013
Participant Information Sheet	20130507	07 May 2013
Protocol for Management of the Database	20130507, v1	07 May 2013
REC application	1	07 May 2013
Summary of Research Programme(s)	20130507, v1	07 May 2013

Research governance

A copy of this letter is being sent to the R&D office responsible for South London and Maudsley NHS Foundation Trust.

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Database managers are advised to provide R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research databases. There is no need to inform Local Research Ethics Committees.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Annual Reports. Please refer to the attached conditions of approval.
c) Amendments. Please refer to the attached conditions of approval.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

08/H0606/71+5	**Please quote this number on all correspondence**

Yours sincerely,

Professor Nigel Wellman
Chair

E-mail: nrescommittee.southcentral-berkshire@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

Approval conditions

Copy to: *South London and Maudsley NHS Foundation Trust*
Mr Mike Denis, South London and Maudsley NHS Foundation Trust

NRES Committee South Central - Oxford C

Attendance at Committee meeting on 28 June 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Leonard Brookes	Consultant to the Pharmaceutical Industry	Yes	
Dr Avinash Gupta	Clinical Research Fellow	Yes	
Mrs Sue Hallett	Paediatric Research Nurse	Yes	
Miss Kate Hicks	Planning Officer (REF)	Yes	
Mrs Rebekah Howe	Lay Member	No	
Mrs Vivienne Laurie	Barrister	Yes	
Mrs Susan Lousada	Lay Member	Yes	
Mr Barry Muir	Lay Member	No	
Mrs Rachael Quinn	Nurse Member	Yes	
Dr David Scott	Pharmacist	Yes	
Dr Sabeena Sharma	Consultant Anaesthetist	Yes	
Dr Surjeet Singh	Clinical Trials Coordinator	Yes	
Dr Laurence Villard	Senior Lecturer/Epidemiologist	No	
Mrs Yael Vinciguerra	Independent Freelances	No	
Professor Nigel Wellman	Professor of Health and Human Sciences	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Cathy Chesham	NRES Management
Ms Rae Granville	Co-ordinator
Miss Kayleigh Morgan	Observer

Written comments received from:

Name	*Position*
Mrs Rebekah Howe	Lay Member

Appendix 2 – GAP Ethical approval

Institute of Psychiatry

at The Maudsley

Ethical Committee (Research)
Research Ethics Co-ordinator
Margaret M Chambers Msc

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KING'S College LONDON
University of London

ETHICAL COMMITTEE (RESEARCH)

RECEIVED 19 SEP 2005

14 September 2005

Prof R Murray
Division of Psychological medicine
PO63
Institute of Psychiatry

Dear Prof Murray

Re: Biological Phenotypes, environment and genes in psychosis (135/05 or 05/Q0706/158)

The Chair of the Ethical Committee (Research) has taken action to approve this study from an ethical point of view.

Please note that this approval is subject to confirmation by the full Committee when it meets on 21 October 2005. Initial approval is given for one year. This will be extended automatically only on completion of annual progress reports on the study when requested by the EC(R). Please note that as Principal Investigator you are responsible for ensuring these reports are sent to us.

Please note that projects which have not commenced within two years of original approval must be re-submitted to the EC(R).

Any serious adverse events which occur in connection with this study should be reported to the Committee using the attached form.

Please quote Study No. 135/05 in all future correspondence with the IOP/SLAM Research Ethics Office.

When corresponding with other LRECs, please quote Study No. **05/Q0706/158**, which is the study number as registered on the national Research Ethics Database.

Yours sincerely,

Margaret M. Chambers

Margaret M Chambers
Research Ethics Coordinator

www.kcl.ac.uk

Appendix 3 – GAP informed consent

Institute of Psychiatry

at The Maudsley

Division of Psychological Medicine,
Section of General Psychiatry

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INFORMATION AND CONSENT FORM

You have been asked to take part in a study being conducted in the South London and Maudsley NHS Trust. Before you decide whether to enter the study, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information and ask any questions if something it is not clear or you wish to know more.

Title : Genetics and Psychiatric illness (GAP)

What are the aims of the study?

In our research project we are interested in identifying what the main risk factors that predispose to psychotis are. In particular, we want to know whether there are any genes that increase the risk of developing a psychotic disorder, either alone or by interacting with environmental factors such as stress, cannabis, and infections. Part of the reason why some people become ill may lay in genetic differences between people, in the same way that we are different in the colour of our eyes, hair etc. To achieve this, we will compare the genetic make-up of people with a diagnosis of psychosis with the make-up of people with similar characteristics but no history of mental health problems.

We also aim to establish whether some genes might influence the course of the illness and response to medication. Some patients experience an improvement of their psychiatric symptoms when they are treated with medications, whereas others do not do so well and/or experience severe side-effects. Therefore we aim to look at

how genes can influence individual differences in response to drug treatment so that we may be able to choose better drugs for each person.

In conclusion, the type of genetic analysis that we carry out is only for research purposes and does not at present produce clinically relevant results.

Why are we asking for your help?

- You have been invited to take part in this study because of the nature of the symptoms that you appear to have been experiencing. During the course of the study approximately 1000 people who have had symptoms like yours will be asked to take part.

What will we ask of you if you take part in the study?

- For this project we will ask from you a small sample of blood, about 20 mls (a few tablespoons full) or cheek swab and saliva samples for metabolic and genetic analysis. We may also use your blood and saliva sample to :
-

  1) Measure the level of hormones and proteins contained in the blood serum and in the saliva.

  2) Look at the expression of some genes of interest in the white cells contained in the blood.

A medically trained researcher will take the blood sample using disposable sterile equipment. It will only take few minutes as for any routine blood sample. If you are unable or unwilling to give a blood sample it is also possible to perform genetic analysis from cheek swab samples, a simple procedure that (we can show you the kit and illustrate the procedure) collects dead cells present in your saliva and in your mouth. From the cheek swab sample we cannot measure level of medication or look at expression of genes, we can only extract a small amount of DNA. Therefore we prefer to ask for a blood sample to guarantee a better quality of our results and make the most out of your generous help.

A researcher will demonstrate how to collect the saliva sample and will provide you with the tubes required. The level of some proteins contained in the saliva can give us an indication of differences in the level of stress experienced by healthy volunteers and people suffering from mental illnesses.

- We will also ask for some of your time to collect clinical and socio-demographic information using standardised research instruments: diagnostic interview, symptoms rating scale, socio-demographic interview and neuropsychological tests.

- If you have already taken part in other research projects at the Institute of Psychiatry, London that involved some of the assessment we are interested in, we will not ask you to undergo them again but we request your permission to use

the existing data.

- Some people within the study will be invited to undergo an MRI scan of the head and of another region of the body (the adrenal gland, a small gland above the kidney). They will be presented with separate information and consent forms for this procedure.

- The sample collection and the clinical assessment will require approximately 3 hours of your time.

- Moreover we would like to contact you again for follow up (up to 24 months) to repeat the above assessments to investigate changes over time.

- We will also reimburse any travel expense related to your participation into the study.

What are the risks?

- The risks involved are those of ordinary blood tests such as small pain and occasionally a small bruise around the area from where the sample has been taken. There is no risk involved in the collection of saliva.

Is Confidentiality guaranteed?

- All personal information about you is regarded as strictly confidential; only researchers belonging to the study team, and not external collaborators, know which sample belongs to whom. All the information about you will be coded; you will not be identifiable in any research outcome.

1) The blood samples first and the DNA samples after extraction will be stored in the Institute of Psychiatry secured laboratory for 5 years.

2) The samples will be coded using bar codes (numbers and letters not referring to your name or date of birth) that will be entered on a secure computerized data base.

3) The clinical information collected on the sample will be securely held in the Institute of Psychiatry building.

The access to the samples and the related information **will** be restricted to the researchers involved in the study. In case of commercial collaborations only the coded data will be shared, therefore no researcher external to the study team will ever have access to personal data concerning participants.

Any future work will pursue aims related to the topic of this project and any extension of the project beyond 5 years, will be subject to review by a research ethics committee.

You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect any of the care and treatment you receive.

What are the benefits for you of taking part?

This is a research project, looking at comparing a group of healthy volunteers with people experiencing their first psychotic episode. As mentioned before, this study will not produce individual test results for any of the data collected. Therefore we cannot offer direct benefits for you. We will be able to provide to all the participants with a general summary of our research, when the project is complete, through a project newsletter. Our research study is also described on the Institute of Psychiatry general website (www.iop.kcl.ac.uk), under the division of Psychological Medicine, Department of General Psychiatry.

Who is funding this project?

- This study is funded by the Maudsley Charitable Fund and the Department of Health.

Thank you very much for your time and once again please ask for more information on both the project and or your illness/symptoms if it is still unclear.

Contact name and telephone number: Dr Marta Di Forti. Tel 0207 848 5352

e.mail :m.diforti@iop.kcl.ac.uk

CONSENT FORM

If you have come to the decision of entering the study after carefully weighting the information provided please read and sign this form.

Title of project: **Genetics and Psychiatric illness (GAP)**

Researcher: **Dr Marta Di Forti, Institute of Psychiatry**

Please tick boxes

1. I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. I understand why the research is being done and the risks involved.

2. I agree to give a sample of blood/cheek swab and saliva samples for research in the above project. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat part of the assessment.

3. I understand that research using the sample I give will involve genetic analysis aimed at understanding the role of genes in disease and response to drugs, that the data produced are for research rather than clinical purposes, and that these results will have no implications for me personally.

4. I understand I will not receive any 'test' results from this study, because the assessment I will undergo, does not produce clinically relevant information but just research data. The project newsletter will describe the general importance of any research results obtained.

5. I give permission for my previous research records to be looked at,

and information from them to be analysed in strict confidence by responsible professional staff from the research team. Researchers external to the study team, collaborating in the project (including commercial collaborations) will only access my coded data.

6. I agree that the samples I have given and the information gathered about me can be examined and stored (for 5 years) at the Institute of Psychiatry. I understand that future research may be performed by researchers other than those who conducted the first project, including researchers from commercial organisations. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial collaborators, will only have access to coded data and not to personal details. Any future research will only persue aims related to the topic of this project,and any extension of the project beyond 5 years, will be subjected to review by a research ethics committee.

7. I consent to the input of coded data obtained from my blood sample and from the information gathered about me into a computer, to be used for statistical analysis and research. I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted.

8. I understand I will not benefit financially if this research leads to the development of a new treatment or medical test but my travel expenses will be reimbursed.

.....	.....	.....
Name of subject	Date	Signature
.....	.....	.....
Name of researcher	Date	Signature

Appendix 4 – Santander study Ethical approval and informed consent

13th March 2014

To whom it may concern,

I can thereby certify that the 'Programa Asistencial de las Fases Iniciales de Psicosis' (PAFIP) has received ethical approval as a data resource for secondary analyses from the Hospital Universitario Marqués de Valdecilla (Santander, Spain) Research Ethics Committee since 2001, including the subsequent renewals to date.

Yours faithfully,

Professor Crespo-Facorro

Consultant Psychiatrist

Head of Division and Project Leader

Correo electrónico:

[Hacer click para escribir la dirección]

Avda. de Valdecilla, s/n
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CONSENTIMIENTO INFORMADO DEL PACIENTE

Protocolo de atención clínica e investigación de los primeros episodios psicóticos de Cantabria (PAFIP)

Se solicita su autorización para ser incluido en un programa de tratamiento en el Servicio de Psiquiatría del Hospital Universitario "Marqués de Valdecilla".

El programa incluye una parte de investigación que implica la realización de algunas pruebas psicológicas, de análisis de laboratorio y de resonancia magnética cerebral, que se repetirán a lo largo de las revisiones y que ayudarán a complementar el estudio de su enfermedad.

Algunas de las pruebas practicadas no son imprescindibles y sirven para complementar el proyecto en su parte investigadora. Aunque Ud. puede beneficiarse de la realización de las mismas, sobre todo, sirven para un mejor conocimiento de la enfermedad que padece.

Ud. participa voluntariamente en este programa y puede retirarse de él sin tener que dar explicación alguna. En este caso, pasaría a recibir el tratamiento especializado convencional.

Este protocolo ha sido aprobado por el Comité Ético del Hospital Universitario "Marqués de Valdecilla", que tiene por misión velar por las normas éticas que regulan los estudios médicos para seguridad de los pacientes participantes en los mismos.

Nombre del participante: _____

He recibido información adaptada a mi nivel de entendimiento de los extremos indicados anteriormente, así como de las posibles alternativas de tratamiento, con sus pros y contras. Estoy satisfecho de la información recibida y de haber obtenido respuestas claras sobre las dudas planteadas.

_____ _____
(Firma del participante) (Fecha)

_____ _____
(Firma del representante legal del participante) (Fecha)

MEDICO INFORMANTE

Yo he explicado y discutido con él paciente o su representante legalmente autorizado los puntos anteriormente expuestos. En mi opinión el paciente ha entendido los objetivos, procedimientos, riesgos, beneficios y obligaciones referentes a su participación en este protocolo.

_____ _____
(Nombre y firma del médico) (Fecha)

Appendix 5 – SAI-E (Kemp & David, 1997)

1. "Do you think you have been experiencing any emotional or psychological changes or difficulties?"	*Often* (thought present most of the day, most days)	
	Sometimes (thought present occasionally)	
	Never (ask why doctors / others think so)	
Notes/Comments:		

2. "Do you think this means there is something wrong with you?" (For example, a nervous condition). *If previous answer was "never" or "no" ask ; "If the doctor(s) and/or others think you have been experiencing emotional or psychological changes or difficulties do you think there must be something wrong with you even though you don't feel it yourself?"*	*Often* (thought present most of the day, most days)	
	Sometimes (thought present occasionally)	
	Never (ask why doctors / others think so)	
Notes/Comments:		

3. "Do you think your condition amounts to a mental illness or mental disorder?"	*Often* (thought present most of the day, most days)	
	Sometimes (thought present occasionally)	
	Never (ask why doctors / others think so)	
Notes/Comments:		

If score '0' on items 2 and 3 proceed straight to item 6 and score items 4 and 5 as '0'.

4. "How do you explain your condition / disorder / illness?"	*Reasonable account given based on plausible mechanisms* (appropriate given social, cultural and educational background, e.g. excess stress, chemical imbalance, family history, etc)	
	Confused account, or overheard explanation without adequate *understanding or "don't know"*	
	Delusional or bizarre explanation	
Notes/Comments:		

If score '0' on items 1, 2 and 3 proceed straight to item 6 and score item 5 as '0'.

5. "Has your nervous/emotional /psychological /mental /psychiatric condition (use patient's term) led to adverse consequences or problems in your life?" (For example, conflict with others, neglect, financial or accommodation difficulties, irrational, impulsive or dangerous behaviour).	*Yes* (with example)	
	Unsure (cannot give example or contradicts self)	
	No	
Notes/Comments:		

6. "Do you think your … condition (use patient's term) or the problem resulting from it warrants (needs) treatment?"	*Yes* (with example)	
	Unsure (cannot give example or contradicts self)	
	No	
Notes/Comments:		

7. Pick the most prominent symptoms <u>up to</u> a maximum of 4. Then rate awareness of each symptom out of 4 as below. (Interviewer to assess which symptoms to rate from previous interviews e.g. highest scoring on PANSS and/or from patient's current presentation).

Examples:

"Do you think that the belief ... is not really / happening (could you be imagining things)?"

"Do you think the 'voices' you hear are actually real people talking, or is it something arising from your own mind?"

"Have you been able to think clearly, or do your thoughts seem mixed up / confused? Is your speech jumbled?"

"Would you say you have been more agitated / overactive / speeded up / withdrawn than usual?"

"Are you aware of any problem with attention / concentration / memory / motivation?"

Symptom 1:	
Symptom 2:	
Symptom 3:	
Symptom 4:	
Mean Score:	

4 = *Definitely* (full awareness)

3 = *Probably* (moderate awareness)

2 = *Unsure* (sometimes yes, sometimes no)

1 = *Possibly* (slight awareness)

0 = *Absolutely not* (no awareness)

Notes/Comments:

8. For each symptom rated above (up to a maximum of 4), ask patient ... "How do you explain ... (false beliefs, hearing voices, thoughts muddled, lack of drive etc.)?"

4 **=** *Part of my illness*

3 **=** *Due to nervous condition*

2 **=** *Reaction to stress / fatigue*

1 **=** *Unsure, maybe one of the above*

0 **=** *Can't say, or delusional / bizarre explanation*

Symptom 1:	
Symptom 2:	
Symptom 3:	
Symptom 4:	
Mean Score:	

Notes/Comments:

9. "How do you feel when people do not believe you? (when you talk about ... delusions or hallucinations)."

That's when I know I'm sick	
I wonder whether something's wrong with me	
I'm confused and I don't know what to think	
I'm still sure despite what others say	
They're lying	

Notes/Comments:

Compliance to treatment/therapy/medication

NOTE: **Patient's primary nurse to rate following three items (A C).**

A. How does patient accept treatment (includes passive acceptance)?	*Often* (may rarely question need for treatment)	
	Sometimes (may occasionally question need for treatment)	
	Never (ask why)	
Notes/Comments:		

B. Does patient ask for treatment unprompted?	*Often* (excludes inappropriate request for medication etc.)	
	Sometimes (rate here if forgetfulness / disorganization leads to occasional requests only)	
	Never (ask why doctors / others think so)	
Notes/Comments:		

C. Summary of compliance to treatment/therapy/medication.	
Complete refusal	**1**
Partial refusal (e.g. refusing depot drugs or accepting only the minimum dose)	**2**
Reluctant acceptance (accepting only because treatment is compulsory or questioning the need for treatment often e.g. every two days)	**3**
Occasional reluctance about treatment (questioning the need for treatment once a week)	**4**

Passive acceptance	**5**
Moderate participation (some knowledge of and interest in treatment and no prompting needed to take the drugs)	**6**
Active participation (ready acceptance, and taking some responsibility for treatment)	**7**
Notes/Comments:	

Appendix 6 – SUMD, 3 general items of the first version (Amador et al., 1993)

1. **Awareness of mental disorder:** In the most general terms, does the subject believe that he or she has a mental disorder?
2. **Awareness of the consequences of mental disorder:** What is the subject's belief regarding the reason(s) he or she has been unemployed, evicted, hospitalized, etc?
3. **Awareness of the effects of medication:** Does the subject believe that medications have diminished the severity of his or her symptoms (if applicable)?

DIRECTIONS:

For each symptom item on the Unawareness Scale, it must first be ascertained that the subject has had the symptom during the time period being rated. Using the ratings you made earlier to determine this. Symptom ratings of 3 or higher are required. Circle the relevant items, then inquire as to the patient's awareness of it.

In order to evidence some awareness, the subject does not have to give precise attributions for symptoms. For example, "I hear voices because of the implant the researchers put in my brain" would constitute a "Somewhat Aware/Unaware" response.

In the current episode column, rate the highest level of awareness during the current exacerbation.

RATING KEY:

unk: UNKNOWN
There is inadequate information to assess.

0: NOT APPLICABLE
Item is not relevant.

1: AWARE
Subject clearly believes that he or she has a mental disorder.

2: SOMEWHAT AWARE/UNAWARE
Subject is unsure about whether he or she has a mental disorder but can entertain the idea.

3: SEVERELY UNAWARE
Subject believes he or she does not have a mental disorder.

Appendix 7 – List of publications based on this thesis

- *Chapter 2 - The role of insight in suicidal behaviour in psychosis: previous research:*
    - **Lopez-Morinigo JD, Ramos-Rios R, David AS, Dutta R.** (2012). Insight in schizophrenia and risk of suicide: a systematic update. *Compr Psychiatry* **53(4):** 313-22.
- *Chapter 3 - Suicide completion by patients with schizophrenia in secondary mental healthcare. Data from the South London and Maudsley (SLaM) Biomedical Research Centre (BRC) Case Register:*
    - **Lopez-Morinigo JD, Fernandes AC, Chang C-K, Hayes R, Broadbent M, Stewart R, David AS, Dutta R.** (2014). Suicide completion in secondary mental healthcare: a comparison study between schizophrenia spectrum disorders and all other diagnoses. *BMC Psychiatry* **14:** 213.
    - **Lopez-Morinigo JD, Ayesa-Arriola R, Torres-Romano B, Fernandes AC, Shetty H, Broadbent M, Dominguez-Ballesteros ME, Stewart R, David AS, Dutta R.** (2016). Risk assessment and suicide by patients with schizophrenia in secondary mental healthcare: a case-control study. *BMJ Open.* doi: 10.1136/bmjopen-2016-011929.
- *Chapter 4 - Suicidal behaviour in early psychosis. Findings from the Genetics and Psychosis (GAP) study (London, UK):*
    - **Lopez-Morinigo JD, Wiffen B, O'Connor J, Dutta R, Di Forti M, Murray RM, David AS.** (2014a). Insight and suicidality in first-episode psychosis: understanding the influence of suicidal history on multiple insight dimensions at first presentation. *Early Interv Psychiatry* **8:** 113–121.
- *Chapter 7 - Suicidal behaviour in early psychosis. Findings from a 3-year follow-up first-episode cohort from Santander (Spain):*
    - **Ayesa-Arriola R, Alcaraz EG, Hernández BV, Pérez-Iglesias R, López Moríñigo JD, Duta R, David AS, Tabares-Seisdedos R, Crespo-Facorro B.** (2015). Suicidal behaviour in first-episode non-affective psychosis: Specific risk periods and stage-related factors. *Eur Neuropsychopharmacol* 25(12): 2278-2288.